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*On Behalf of Plaintiffs Steering Committee*

**UNITED STATES DISTRICT COURT**
**NORTHERN DISTRICT OF CALIFORNIA**
**(SAN FRANCISCO DIVISION)**

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|---|---|
| IN RE: VIAGRA (SILDENAFIL CITRATE) AND CIALIS (TADALAFIL) PRODUCTS LIABILITY LITIGATION | Civil Case No.: 3:16-md-02691-RS<br>MDL No.: 2691 |
| This Document Relates to: ALL ACTIONS | **Hearing Date: June 4-7, 2019**<br>**Time: 10:00 a.m.** |

**PLAINTIFFS' MOTION TO EXCLUDE CERTAIN OF DEFENSE EXPERTS' OPINIONS**

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## ISSUE TO BE DECIDED

Whether the testimony presented Defendants' experts is both relevant and scientifically reliable under the standard set forth in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993) and FED. R. EVID. 702.

## INTRODUCTION

Plaintiffs have met their general causation burden by providing relevant, reliable testimony demonstrating that PDE5 inhibitors sildenafil and tadalafil[1] have "the capacity to cause" melanoma progression. *In re Hanford Nuclear Reservation Lit.*, 292 F.3d 1124, 1133 (9th Cir. 2002). Epidemiological studies have repeatedly demonstrated statistically significant associations between use of PDE5 inhibitors and the progression of melanoma. Studies that analyze the mechanisms of action of PDE5 inhibitors and melanoma demonstrate plausible biological explanations for how PDE5 inhibition can (and does) bring about melanoma development. Plaintiffs have provided ample evidence of this alarming link that is sufficient to establish general causation.

To convince this Court otherwise, Pfizer Inc. ("Pfizer") and Eli Lilly & Company ("Eli Lilly") (collectively "Defendants") offer testimony from nine experts who repeatedly employ unreliable methodology and disregard basic scientific principles. Despite the Ninth Circuit's "liberal thrust favoring admission" of expert testimony, the opinions offered by Defendants' experts amount to nothing more than "junk science" that merit exclusion. *Estate of Barabin v. AstraJohnson, Inc.*, 740 F.3d 457, 463 (9th Cir. 2014).

In this Brief, Plaintiffs address the following topics:

(1) An overview of melanoma, the injury linked to sildenafil and tadalafil;

(2) A discussion of the available epidemiological evidence demonstrating the statistically significant associations between the use of sildenafil and tadalafil and the development of melanoma, as well as the standards for admissibility of expert testimony on epidemiology;

[1] Viagra and Revatio are brand names for the drug sildenafil or sildenafil citrate. Cialis and Adcirca are brand names for the drug tadalafil. As discussed in more detail below, these drugs inhibit the enzyme phosphodiesterase type-5 (PDE5) and more specifically, PDE5A. They are in a class of drugs known as PDE5 inhibitors.

(3) A discussion of the literature demonstrating the biological mechanisms of action by which sildenafil and tadalafil bring about melanoma progression; and

(4) Plaintiffs' arguments in support of its request that the Court exclude testimony by Defendants' experts that do not meet the standards for admissibility in the Ninth Circuit.

## BACKGROUND

### I. MELANOMA SKIN CANCER—THE INJURY LINKED TO SILDENAFIL AND TADALAFIL.

All Plaintiffs in this litigation have suffered from melanoma, in some cases resulting in death, exacerbated by their use of sildenafil and/or tadalafil. Melanoma is the deadliest form of skin cancer, causing the majority of skin cancer deaths.[2] Its rates have risen over the past 30 years, and the American Cancer Society estimated that 2018 would see approximately 91,270 new melanoma diagnoses and that over 9,300 people would die of the cancer.[3]

Melanoma is a cancer that derives from melanocytes—cells at the bottom of the epidermis that are present in normal skin. Upon the acquisition of genetic changes (mutations), melanocytes gain the ability to grow more rapidly and invade into deeper parts of the skin and beyond.[4] Melanomas are characterized by growth and invasion—they typically begin in moles (nevi), then grow larger and move (invade) over time. They can also develop de novo in the skin. It can be difficult to reliably distinguish melanomas from normal moles, raising the likelihood that pre-neoplastic moles and early melanomas exist as a continuum on normal skin, waiting for the right stimulus to grow. *See, e.g.*, PX 1, Bishop *et al.*, *The Prevention, Diagnosis, Referral & Management of Melanoma of the Skin: Concise Guidelines*, 7 CLINICAL MED. 283 (2007); PX 2, Goldstein & Tucker, *Dysplastic Nevi & Melanoma*, 22 CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION 528 (2013).

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[2] *Types of Skin Cancer,* AM. ACAD. OF DERMATOLOGY, https://www.aad.org/public/spot-skin-cancer/learn-about-skin-cancer/types-of-skin-cancer (last visited Jan. 1, 2019).

[3] *Key Statistics for Melanoma Skin Cancer*, AM. CANCER SOC'Y, https://www.cancer.org/cancer/melanoma-skin-cancer/about/key-statistics.html (last visited Jan. 1, 2019).

[4] *What Is Melanoma Skin Cancer?,* AM. CANCER SOC'Y, https://www.cancer.org/cancer/melanoma-skin-cancer/about/what-is-melanoma.html; *see also* JX 9, Haq Rpt. at 10, Figure 1.

Melanoma normally takes many years to develop from premalignant nevi into an identifiable and diagnosable tumor. Once a tumor does develop, it can lay dormant for decades or slowly progress within the skin or in the lymph nodes. *See, e.g.*, PX 3, Ossowski & Aguirre-Ghiso., *Dormancy of Metastatic Melanoma*, 23 PIGMENT CELL MELANOMA RES. 41 (2010). As Plaintiffs' experts agree, the scientific evidence demonstrates that these early stage or dormant melanomas can be reactivated to grow by an environmental trigger or a pharmacologic stimulus from PDE5 inhibitors, like tadalafil or sildenafil. *See, e.g., id.*; PX 4, Martincorena *et al., Tumor Evolution. High Burden & Pervasive Positive Selection of Somatic Mutations in Normal Human Skin*, 348 SCI. 880 (2015); PX 5, Shain *et al., The Genetic Evolution of Melanoma from Precursor Lesions*, 373 NEW ENG. J. MED. 1926 (2015); JX 85, Arozarena *et al., Oncogenic BRAF Induces Melanoma Cell Invasion By Downregulating the cGMP-Specific Phosphodiesterase PDE5A*, 19 CANCER CELL 45 (2011); JX 87, Dhayade *et al., Sildenafil Potentiates a cGMP-Dependent Pathway to Promote Melanoma Growth*, 14 CELL REPORTS 2599 (2016).

Because the survival rate for melanoma patients plummets as the disease progresses,[5] any agent that promotes rapid progression carries severe consequences. Melanoma survivors have an approximately 9-fold increased risk of developing subsequent melanoma compared with the general population.[6] As described below, multiple studies published in well-respected, peer-reviewed journals demonstrate that sildenafil and tadalafil are capable of causing melanoma progression.

## II. EPIDEMIOLOGICAL STUDIES HAVE REPEATEDLY DEMONSTRATED STATISTICALLY SIGNIFICANT ASSOCIATIONS BETWEEN USE OF SILDENAFIL AND TADALAFIL WITH THE DEVELOPMENT OF MELANOMA.

In this case, a significant body of scientific literature demonstrates that sildenafil and tadalafil can and do cause the development of melanoma cancer. At least nine observational studies and six meta-analyses have examined the association between PDE5 inhibitor use and the development of malignant

[5] *Staging Melanoma,* AM. ACAD. DERMATOLOGY, http://skinmelanoma.com/understanding-skin-melanoma/staging-your-melanoma/ (last visited Jan. 9, 2019) (22.5% 5 year survival rate for melanoma that has already metastasized versus 98.4% 5 year survival rate for a localized melanoma).

[6] *Melanoma Recurs After 10 Years in More than 6 Percent of Patients,* AM. C. SURGEONS, https://www.facs.org/media/press%20releases/jacs/melanoma0613 (last visited Jan. 9, 2019).

melanoma.[7] All find associations between PDE5 inhibitor use and melanoma, and most find statistically significant results in either primary or secondary analyses. The seminal, prospective cohort study, demonstrates a statistically significant near doubling of the risk. Five others show statistically significant increased risks in their primary results, with one demonstrating a near tripling of the risk for chronic users of sildenafil or tadalafil.

Below, we first address the legal standards and principals for epidemiology and a causal assessment, and then discuss the available epidemiological evidence.

**A. Epidemiology: Exposure, Association to Disease, Risk, Significance, and Causation.**

Epidemiology "studies the incidence, distribution, and etiology of disease in human populations." *In re Roundup Prods. Liab. Litig.*, 2018 U.S. Dist. LEXIS 114760, at *85 (N.D. Cal. July 10, 2018); *Horwin v. Am. Home Prods.*, 2003 U.S. Dist. LEXIS 28039, at *14 (C.D. Cal. May 9, 2003); *see Cagle v. Cooper Cos. (In re Silicone Gel Breasts Implants Prods. Liab. Litig.)*, 318 F. Supp. 2d 879, 892 (C.D. Cal.

[7] JX 90, Li *et al., Sildenafil use and increased risk of incident melanoma in US men: a prospective cohort study*, 174 JAMA 964 (2014); JX 93, Loeb *et al., Use of Phosphodiesterase Type 5 Inhibitors for Erectile Dysfunction and Risk of Malignant Melanoma*, 313 JAMA 2449 (2015); JX 91, Lian *et al., Phosphodiesterase Type 5 Inhibitors and the Risk of Melanoma Skin Cancer*, 70 EUR. UROLOGY 808 (2016); JX 94, Matthews *et al., Phosphodiesterase Type 5 Inhibitors and Risk of Malignant Melanoma: Matched Cohort Study Using Primary Care Data from the UK Clinical Practice Research Datalink*, 13 PUB. LIBR. SCI. MED. 1 (2016); JX 101, Boor *et al., Melanoma in Men Treated with PDE5A Inhibitors: A Report from the RADAR Project*, 74 J. AM. ACAD. DERMATOLOGY AB190 (May 2016); JX 96, Pottegård *et al., Use of Sildenafil or Other Phosphodiesterase Inhibitors and Risk of Melanoma*, 115 BRITISH J. CANCER 895 (2016); JX 109, Ma *et al., (Abstract) Sildenafil use & risk of malignant melanoma: A population based case-control study (1998-2010).* J. AM. ACAD. DERMATOLOGY (2017); JX 97, Shkolyar *et al., Risk of melanoma with phosphodiesterase type 5 inhibitor use among patients with erectile dysfunction, pulmonary hypertension, and lower urinary tract symptoms*, 15 J. SEXUAL MED. 982 (2018); PX 6, Nardone *et al., Chronic Daily Dosing of PDE5 Inhibitors (Sildenafil or Tadalafil) for Pulmonary Hypertension & Risk of Subsequent Melanoma: A Report from the RADAR Project*, 79 J. AM. ACAD. DERMATOLOGY AB72 (Sept. 2018); JX 99, Wang *et al., Relation of Phosphodiesterase Type 5 Inhibitors and Malignant Melanoma: A Meta-Analysis and Systematic Review*, 8 ONCOTARGET 46461 (2017); JX 92, Loeb *et al., Meta-Analysis of the Association Between Phosphodiesterase Inhibitors (PDE5Is) and Risk of Melanoma*, 109 J. NAT'L CANCER INST. 1 (2017); JX 98, Tang *et al., Phosphodiesterase type 5 inhibitors and risk of melanoma: A meta-analysis*, 77 J. AM. ACAD. DERMATOLOGY 480 (2017); JX 89, Han *et al., Use of phosphodiesterase type 5 inhibitors and risk of melanoma: a metaanalysis of observational studies*, 11 ONCOTARGETS & THERAPY 711 (2018); JX 88, Feng *et al., Are phosphodiesterase type 5 inhibitors associated with increased risk of melanoma? A systematic review and meta-analysis*, 97 MED. 1 (2018); JX 86, Deng *et al., Association between phosphodiesterase type 5 inhibitors use and risk of melanoma: a meta-analysis*, 65 NEOPLASMA 216 (2018).

April 22, 2004); *see also In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 187 (S.D.N.Y. 2009) ("[Epidemiology studies] relationship between exposures and diseases in large populations"). To establish causation, epidemiologists conduct studies to determine whether exposure to an agent is associated with an increased risk of developing a disease. *See Roundup*, 2018 U.S. Dist. LEXIS 114760, at *85; *Fosamax*, 645 F. Supp. 2d at 187.

Epidemiological studies are probative of general causation. *See Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 882 (10th Cir. 2005); *Roundup*, 2018 U.S. Dist. LEXIS 114760, at *85; *In re Bextra & Celebrex Mktg. Sales Prac. & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1172 (N.D. Cal. 2007); *Cagle*, 318 F. Supp. 2d at 892. "Unquestionably, epidemiological studies provide the best proof of general association of a particular substance with particular effects." *Brasher v. Sandoz Pharm. Corp.*, 160 F. Supp. 2d 1291, 1296 (N.D. Ala. 2001). Yet, although these studies offer "powerful evidence" of causation, epidemiological studies are not required to prove causation. *Wells v. Ortho Pharm. Corp.*, 788 F.2d 741, 745 (11th Cir. 1986); *see generally, Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986 (8th Cir. 2001); *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193 (10th Cir. 2002); *In re Neurontin Mktg., Sales Prac. & Prods. Liab. Litig.*, 612 F. Supp. 2d 116, 132 (D. Mass. 2009).

Epidemiological studies often identify an association between an individual's exposure to a particular agent and the subsequent development of a disease. *See Horwin*, 2003 U.S. Dist. LEXIS 28039, at *14 (citing *Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1356 (N.D. Ga. March 1, 2001)). To determine the existence of an association, epidemiologists calculate ratios by comparing exposed and unexposed subjects in relation to the disease outcome. *Caraker v. Sandoz Pharms. Corp.*, 188 F. Supp. 2d 1026, 1031 (S.D. Ill. 2001). This ratio, or "relative risk," is obtained by dividing the number of exposed subjects who contract the disease by the number of unexposed subjects also contracting it. *Cagle*, 318 F. Supp. 2d at 892. A relative risk greater than 1.0 demonstrates a positive association, suggesting that a particular agent has the capacity to cause the disease. *Bextra & Celebrex*, 524 F. Supp. 2d at 1172. While relative risk is a commonly used calculation, epidemiologists frequently use other measurements to convey risk, such as odds and risk ratios, which are calculated differently but are practically interchangeable.

"The possible role of chance must always be considered in evaluating the results of an epidemiology study." *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 592 (D.N.J. 2002), *aff'd*, 68 F. App'x 356 (3d Cir. 2003). Statistical significance is "an important metric to distinguish between results supporting a true association and those resulting from mere chance." *In re Zoloft Prods. Liab. Litig.*, 858 F.3d 787, 793 (3d Cir. 2017). Nevertheless, an overemphasis on statistical significance alone would be misplaced: "it is a commonly held belief in the field of epidemiology that a statistical significance is neither obligatory no[r] appropriate to use as a requirement for drawing inferences from epidemiological data." *In re Trasylol Prods. Liab. Litig.*, 2010 U.S. Dist. LEXIS 142228, at n.13 (S.D. Fla. 2010). Courts frequently permit experts to testify as to causation based on evidence other than statistical significance. *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27, 40-41 (2011) ("lack of statistically significant data does not mean that medical experts have no reliable basis for inferring a causal link between a drug and adverse events"); *In re Chantix (Varenicline) Products Liab. Litig.*, 889 F. Supp. 2d 1272, 1286 (N.D. Ala. 2012).

Finally, to analyze whether a statistical association is causal, epidemiologists consider several factors, commonly referred to as the Bradford-Hill criteria. *Amorgianos v. AMTRAK*, 137 F. Supp. 2d 147, 168 (E.D.N.Y. 2001). This generally accepted method assesses nine factors used to determine whether causation exists between a particular agent and disease. *See In re Breast Implant Litig.*, 11 F. Supp. 2d 1217 n.5 (D. Colo. 1998) ("Once an association has been shown, the Bradford-Hill criteria are applied to determine whether there is actually a cause and effect"). The nine factors are: (1) Strength of Association, (2) Consistency, (3) Specificity, (4) Temporality, (5) Biological Gradient (Dose-Duration Response), (6) Biological Plausibility, (7) Coherence (coherence with existing knowledge), (8) Experiment, and (9) Analogy. JX 102, Austin Bradford Hill, *The Environment and Disease: Association or Causation?*, 58 PROC. ROYAL SOC'Y MED. 295 (1965). Application of the criteria often requires an expert to consider more than the epidemiology literature. *See Roundup*, 2018 U.S. Dist. LEXIS 114760, at *122. Particularly, the Bradford-Hill framework allows experts the flexibility of reviewing all available evidence that may support or disprove causation. *See id.* Thus, a "broad survey of the available evidence is neither unusual

in expert testimony nor necessarily inappropriate." *Id.*; *see, e.g.*, *Milward v. Acuity Specialty Products Group, Inc.*, 639 F.3d 11, 19-20 (1st Cir. 2011); *Neurontin*, 612 F. Supp. 2d at 158-59.

**B. Here, Epidemiological Studies Demonstrate Sildenafil and Tadalafil Cause the Development of Melanoma Cancer.**

In this case, the available epidemiology demonstrates that sildenafil and tadalafil, via the inhibition of PDE5, cause the development of melanoma.

Every observational study includes a positive association (relative risk, or other measurement of risk, greater than 1.0). The consistency of results provides strong evidence of a causal association between an increased risk of melanoma and the use of PDE5 inhibitors. The seminal observational study, a prospective cohort study from Li 2014 found a "significantly elevated risk of invasive melanoma" in patients who had recently used sildenafil (multivariate-adjusted HR (hazard ratio) 1.84 (95% CI, 1.04-3.22)). JX 90. Patients who had used sildenafil at any time had an even higher risk of melanoma (HR 1.92 (95% CI, 1.14-3.22)). *Id.* This finding reflects a 92% increase in the risk of melanoma in men who used sildenafil compared to those who did not. This near doubling of the risk is evidence of a strong association, especially since PDE5 inhibition via sildenafil and tadalafil acts as an accelerant of melanoma disease progression. Indeed, the association is understated:

> For most chronic diseases of adulthood, it is not possible for epidemiologic studies to distinguish between acceleration of disease and causation of a new disease. If, in fact, acceleration is involved, the relative risk from a study will ***understate*** the probability that exposure accelerated the occurrence of the disease.

PX 37, *Reference Manual on Scientific Evidence*,[8] at 612, 614-615 (3d ed.) (hereinafter "*RMSE*") (emphasis added).

Two additional studies followed shortly thereafter, both confirming the association. Loeb 2015, a nested case-control study, found "a significantly increased risk of melanoma remained in men with filled PDE5i prescriptions (OR 1.21 [95% CI, 1.08-1.36]), as compared to controls with no filled PDE5 inhibitor prescriptions." JX 93. In Matthews 2016, the study found a small positive association between PDE5 inhibitor use and melanoma (HR 1.14 (95% CI 1.01-1.29, $p$=0.04)). JX 94. Both studies were carried out

[8] The relevant sections cited in this brief are included in PX 37.

by independent investigators from different countries using unique designs and populations, and all consistently showed an association between PDE5 inhibitor use and an increased risk of melanoma.

More observational studies followed. Lian 2016 found a positive overall association with a statistically significant increased risk for melanoma among those who had received seven or more prescriptions and among those who had greater than twenty-five pills (HR 1.30 (95% CI, 1.01-1.69) and HR 1.34 (95% CI, 1.04-1.72), respectively). JX 91. Similarly, Pottegård 2016 observed a significant association in patients reporting a "high use" of PDE5 inhibitors (OR 1.28 (95% CI, 1.05-1.56)). JX 96. Likewise, Shkolyar 2018 found a slight association between higher volume PDE5 inhibitor use and development of melanoma. JX 97.

A set of three abstracts presented to the American Academy of Dermatology all found statistically significant increased risks of melanoma after sildenafil and tadalafil use. In Boor 2016, researchers from Northwestern University observed an increased risk for both sildenafil (OR 1.6 (95% CI, 1.11-2.31, p=0.01) and tadalafil (OR 2.07 (95% CI, 1.48-2.89, p< 0.001). JX 101. In Ma 2017, researchers from the Mayo Clinic likewise found an increased risk in men taking sildenafil (univariate analysis OR 2.02 (95% CI, 1.32-3.09), multivariate analysis OR 2.38 (95% CI, 1.49-3.81)). JX 109. Most recently, in Nardone 2018, researchers found the highest yet increased risk of melanoma in patients who used sildenafil or tadalafil chronically for treatment of pulmonary hypertension (OR 2.98 (95% CI, 1.15-7.75, P=0.02)). PX 6. Each of these abstract studies were published in a respected journal, all "solicited, blind reviewed, and graded by peer review" for selection as an exhibit and discussion at the summer or annual meeting of the American Academy of Dermatology. *See* PX 7-9 (American Academy of Dermatology presentations of the Boor 2016, Ma 2017, and Nardone 2018 studies).

Meta-analyses also support a causative link between PDE5 inhibitor use and melanoma. A meta-analysis is an epidemiological study that combines the results of individual studies "to arrive at a single figure to represent the totality of the studies reviewed." *Mullins v. Premier Nutrition Corp.*, 178 F. Supp. 3d 867, 884 (N.D. Cal. 2016) (quoting PX 37, *RMSE at* 607 ("This system of methodically reviewing the literature often includes weighing the clinical studies and examining the cause of heterogeneity among the pooled clinical trials")).

Six meta-analyses have been conducted to date, each revealing a statistically significant association between PDE5 inhibitor use and an increased risk of melanoma. JX 92, Loeb 2017; JX 98, Tang 2017; JX 99, Wang 2017; JX 86, Deng 2018; JX 89, Han 2018; JX 88, Feng 2018. The point estimates in these studies ranged from 1.11-1.13. Further, several of these studies also reported statistical significance in subgroup analyses. *See, e.g.*, JX 86, Deng 2018 (statistically significant increased risk with single prescriptions (RR 1.20, 95% CI 1.06-1.35), medium prescriptions (1.15, 95% CI 1.01-1.30), and high prescriptions (RR 1.18, 95% CI 1.05-1.34)); JX 89, Han 2018 (statistically significant increased risk of malignant melanoma for sildenafil alone (RR 1.26 [1.07-1.50])); JX 88, Feng 2018 (increased risk of localized melanoma (1.22. 95% CI 1.04-1.43)).

## III. ROBUST SCIENTIFIC EVIDENCE DEMONSTRATES THE BIOLOGICAL MECHANISM BY WHICH SILDENAFIL AND TADALAFIL CAN CAUSE THE DEVELOPMENT OF MELANOMA CANCER.

A robust body of science demonstrates the biological mechanism by which PDE5 inhibition can bring about the progression of melanoma cells via the mitogen-activated protein kinase (MAPK) pathway—a pathway known to be activated in human melanoma cells. This evidence establishes the Bradford-Hill factor of "biological plausibility"—the question of whether an observed association is consistent with existing biological and pharmacological knowledge. PX 37, *RMSE* at 604. A causation opinion should be premised first on "whether the disease can be related to chemical exposure by a biologically plausibility theory. *See also id.* at 661.[9]

The weight of the biological plausibility factor depends on the extent of scientific knowledge about the cellular and subcellular mechanisms through which the disease process works. PX 37, *RMSE* at 605. A finding of biological plausibility does not, however, require scientific certainty. *See In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1308 (N.D. Fla. 2018) (citing *Daubert*, 509 U.S. at 590.) ("Of course, it would be unreasonable to conclude that the subject of scientific testimony must be 'known' to a certainty; arguably, there are no certainties in science."). When biological plausibility exists,

[9] "Biologically plausible theory" is defined as "[a] biological explanation for the relationship between exposure to an agent and adverse health outcomes." *Id.* at 680 (*Ref. Guide on Toxicology*).

it "lends credence to an inference of causality." PX 37, *RMSE* at 604. *See also Abilify*, 299 F. Supp. 3d at 1308.

In this case, the mechanism of action by which PDE5 inhibitors sildenafil and tadalafil bring about melanoma progression is the same mechanism of action by which they bring about their intended therapeutic effect of producing an erection.

**A. Sildenafil and Tadalafil Achieve Their Therapeutic Effect Through Inhibition of PDE5.**

Sildenafil and tadalafil are inhibitors of an enzyme called PDE5. The PDE5 enzyme is responsible for degradation of an intracellular chemical signal called cyclic guanosine monophosphate (cGMP).

An erection involves the release of nitric oxide (NO) during sexual stimulation. NO then activates the guanylate cyclase enzyme, resulting in increased levels of cGMP. Increased levels of cGMP, in turn, produce smooth muscle relaxation and allow increased blood flow to the penis, causing an erection.

Men with erectile dysfunction do not produce sufficient levels of NO during sexual stimulation resulting in low cGMP production. When cGMP production is insufficient, further degradation of cGMP by PDE5 results in inadequate levels of cGMP needed to maintain an erection.

The use of sildenafil and tadalafil enhances the effect of NO by inhibiting PDE5. In the presence of sexual stimulation (which releases NO), sildenafil and tadalafil inhibit PDE5 which in turn causes increased levels of cGMP in the corpus cavernosum by lessening PDE5's natural degradation of cGMP. This results in smooth muscle relaxation and increased blood flow to the penis, causing an erection. *See* PX 38, Sildenafil Label, PX 39, Tadalafil Label; *see also* PX 40, Ghofrani *et al., Sildenafil: From Angina to Erectile Dysfunction to Pulmonary Hypertension & Beyond*, 5 NAT. REV. DRUG DISCOVERY 689 (2006).

**B. PDE5 is Present in Human Melanocytes and Melanoma Cells.**

In addition to being present in the corpus cavernosum, PDE5 is also present in melanoma cells and normal human melanocytes (NHMs), the precursor cells to melanoma. *See, e.g.,* PX 10, Drees *et al., 3',5'-Cyclic Nucleotide PDE in Tumor Cells as Potential Target for Tumor Growth Inhibition*, 53 CANCER RES. 3058 (1993); JX 112, Murata *et al., Expression & Role of PDE5 in Human Malignant Melanoma Cell Line*, 30 ANTICANCER RES. 355 (2010); JX 85, Arozarena 2011; JX 87, Dhayade 2016. Interestingly,

research has demonstrated that PDE5 levels decrease as melanoma cells progress when compared to levels in NHMs—strongly suggesting drugs that inhibit PDE5 could plausibly accelerate melanoma progression. For example, the BRAF mutation, found in approximately 50 percent or more of patients, is the most common mutation in melanoma cells. PX 11, Mitra *et al., Melanoma & Viagra: An Unexpected Connection*, 24 PIGMENT CELL MELANOMA RES. 16 (. 2011). In 2009, Packer *et al.* examined the molecular consequences of constitutively active BRAF. JX 115, Packer *et al., Identification of Direct Transcriptional Targets of (V600E) BRAF/MEK Signaling in Melanoma*, 22 PIGMENT CELL RES. 785 (2009). They performed an analysis to examine gene expression changes in response to oncogenic BRAF and identified PDE5 as one of the genes down-regulated (inhibited) in melanoma cells in response to BRAF activation. *Id.*

Consistent with the conclusion that PDE5 inhibitors can plausibly impact both NHMs and melanoma cells, Arozarena 2011 further demonstrates that both NHMs and melanoma cells can and do express levels of PDE5. JX 85 at 47, Figure 1. In Arozarena 2011, PDE5 levels in developed melanoma cells were often lower compared to levels in NHMs, supporting the premise that PDE5 levels decrease as melanocytes progress to melanomas and melanomas progress themselves. *Id.* at Figure 1, Figure S2. This process is a strong signal that PDE5 inhibition, via sildenafil or tadalafil, could plausibly play a role in melanoma progression:

> [Arozarena 2011] found that PDE5A was downregulated in a substantial collection of melanoma lines expressing oncogenic BRAF, indicating that this is an inherent phenotype and may provide a biomarker for enhanced invasiveness and poor prognostic outcome. Indeed, in this regard, primary [melanoma] tumors showed higher overall PDE5A expression than did metastatic tumors.

JX 106, Houslay, *Hard Times for Oncogenic BRAF-Expressing Melanoma Cells*, 19 CANCER CELL 3, 4 (2011).[10]

[10] PDE5 and PDE5A are used interchangeably in this brief.

### C. Reliable Scientific Studies Demonstrate that Inhibition of PDE5 Results in Melanoma Progression.

#### 1. Arozarena 2011.

Arozarena 2011 shows dramatically increased invasiveness of melanoma cells when PDE5 is downregulated both pharmacologically and genetically. The authors summarize their findings, stating that "[PDE5] is not a therapeutic target in melanoma, and our data even raise the possibility that [PDE5 inhibitor] drugs could promote melanoma metastasis." JX 85 at 55. The authors highlight the importance of their findings explaining that "patients with small primary tumors or stage I/II disease often already have distant secondary metastases, and melanoma cells can rapidly evolve to become invasive (Balch & Cascinelli 2001), so any acceleration to this process is undesirable." *Id.*

The study is comprised of a robust collection of experiments demonstrating the impact on melanoma cells when PDE5 levels are either increased or decreased. *Id.* at 46-50. In one experiment utilizing two melanoma cell types found to have no detectable levels of PDE5 expression, the genetic addition of PDE5 to these cell types resulted in a decrease in invasion levels in a statistically significant manner compared to control to test. *Id.* In a related experiment utilizing two melanoma cell types found to have detectable PDE5A expression, the genetic reduction of PDE5 in these cell types resulted in an increase in invasion levels in a statistically significant fashion (4 to 14-plus fold increase in invasion) compared to control. *Id.* Finally, the authors treated these same melanoma cells that expressed PDE5 with Viagra, Cialis, and Levitra—this pharmacological reduction of PDE5 in these melanoma cells resulted in increased invasion levels in a statistically significant fashion (about 3-4 fold increase in invasion). *Id.*[11]

These findings demonstrate consistent results from the effects of raising or lowering PDE5 levels in melanoma cells, whether done pharmacologically or genetically. The totality of evidence found in

[11] The authors note that "BRN2 upregulation is associated with increased melanoma cell invasion (Pinner 2009)." Building upon this knowledge, Arozarena 2011 found that "BRN2 binds to the PDE5A promoter and using reporter constructs show that one of the putative BRN2-binding sites in the promoter is essential for the suppression of PDE5A transcription by oncogenic BRAF." JX 85, Arozarena 2011 at 53; *see also id.* at Figure 2 ("BRN2 Downregulates PDE5A").

Arozarena 2011 demonstrates that increased invasion levels in certain melanoma cells do in fact result from the presence and subsequent decrease of PDE5 specifically, as opposed to some other mechanism.[12]

The authors go further to describe and demonstrate the biologic processes for how and why PDE5 inhibition brings about melanoma progression. To summarize: PDE5 downregulation, via PDE5 inhibitor drugs or genetic knockdown, impacts the MAPK pathway along with BRN2, thereby increasing intracellular cGMP levels and promoting a "dramatic increase in melanoma invasion" both *in vitro* and *in vivo*.[13] *Id.* at 45, 53-55; JX 106, Houslay 2011 at 3. Significantly, many years before Arozarena 2011 was published, the MAPK pathway was understood to be one of "the main pathways involved in melanoma initiation, progression and maintenance." PX 12, Gray-Schopfer *et al., Melanoma Biology & New Targeted Therapy*, 445 NAT. 851 (2007) at Figure 2. In fact, MEK inhibitors are drugs developed to treat melanoma by inhibiting of the MAPK pathway. *See id.*

The clinical implication of Arozarena 2011 "is whether patients taking PDE5A inhibitor drugs could be inadvertently increasing the invasive potential of melanotic lesions." PX 11, Mitra 2011 at 17. While later stage melanomas may have very low or absent PDE5A levels, it is very concerning that "patients with very early-stage melanomas (that may not yet have been picked up clinically) may still express PDE5A at clinically meaningful levels (as suggested by [Arozarena's] tissue microarray data), and these melanomas may be encouraged to switch to a more invasive state with PDE5A inhibition." *Id.* In agreement with the conclusions drawn by Arozarena 2011, other scientists have recognized that the "elegant study thus provides an important insight into the mechanism whereby oncogenic B-RAF

[12] The authors also performed several *in vivo* experiments. These experiments used genetic methods of altering PDE5 expression and similarly found that PDE5 regulates melanoma invasion *in vivo*. The authors also tested pharmacologic PDE5 inhibitors (Viagra, Cialis, Levitra) *in vivo*, but the results were not statistically significant. *Id.* at 52-54. The authors' failure to test if the dose of medication given to the mice they tested was sufficient to actually cause the effect they were testing for is an oversight which complicates any interpretation of their *in vivo* data results. *See id.*

[13] The authors note that prior studies have shown the role of Ca2+ in regulating breast cancer cell migration and metastasis (Yang 2009). They confirm that their study results establish the role of PDE5 in regulating melanoma cell invasion by "regulating intracellular Ca2+ through cGMP." They explain that the study "show[s] that cGMP and Ca2+ levels are inversely correlated with PDE5A expression in melanoma cells and that cGMP elevates Ca2+ in 501mel [melanoma] cells." Further noting that "artificially increasing either cGMP or Ca2+ using a variety of pharmacologic agents was sufficient to induce 501mel [melanoma] cell invasion." *Id* at 53.

promotes invasiveness in melanoma cells through a mechanism that pivotally involved PDE5A downregulation and elevation of cGMP levels (Figure 1)." JX 106, Houslay 2011 at 4.

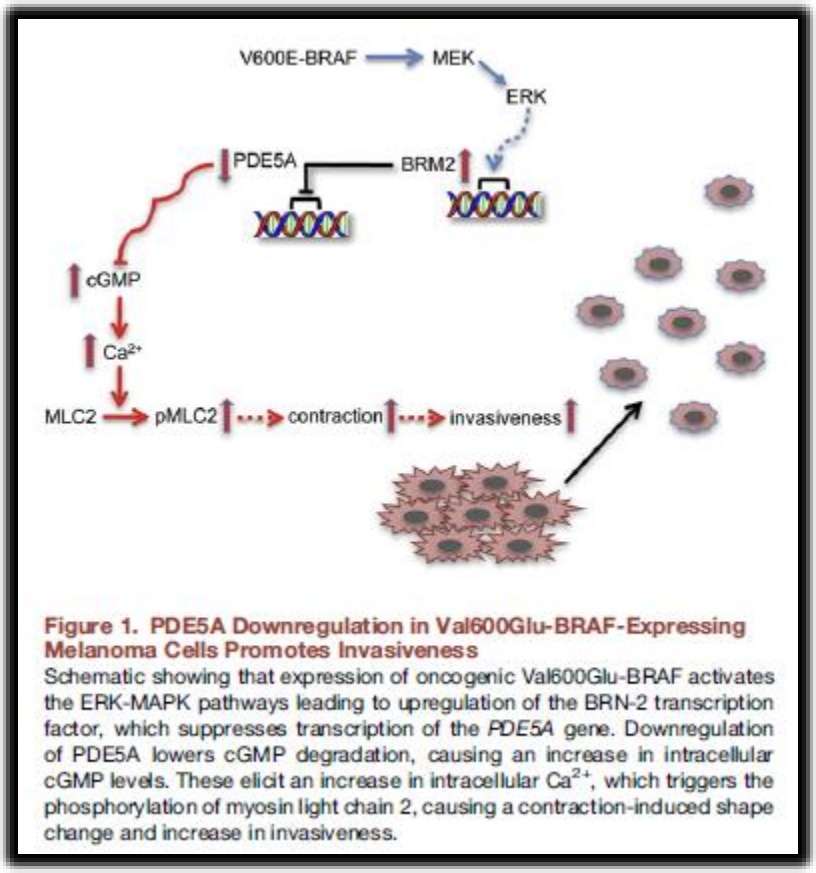


**Figure 1. PDE5A Downregulation in Val600Glu-BRAF-Expressing Melanoma Cells Promotes Invasiveness**
Schematic showing that expression of oncogenic Val600Glu-BRAF activates the ERK-MAPK pathways leading to upregulation of the BRN-2 transcription factor, which suppresses transcription of the *PDE5A* gene. Downregulation of PDE5A lowers cGMP degradation, causing an increase in intracellular cGMP levels. These elicit an increase in intracellular $Ca^{2+}$, which triggers the phosphorylation of myosin light chain 2, causing a contraction-induced shape change and increase in invasiveness.

*Id* at Figure 1 (depicting the mechanism of action by which decreased PDE5A leads to invasiveness, as demonstrated in Arozarena 2011).

**2. Dhayade 2016.**

In 2016, Dhayade *et al.*, from the University of Tübingen's cell signaling laboratory lead by cGMP researcher Dr. Robert Feil,[14] released additional scientific research titled "Sildenafil Potentiates a cGMP-Dependent Pathway to Promote Melanoma Growth." JX 87. The study analyzed the underlying

[14] Dr. Feil's laboratory investigates cGMP signaling in cell growth and survival. *See Prof. Dr. Robert Feil*, U. TÜBINGEN, https://uni-tuebingen.de/fakultaeten/mathematisch-naturwissenschaftliche-fakultaet/fachbereiche/interfakultaere-institute-und-zentren/ifib/arbeitsgruppen/gruppen-a-f/feil/lab-members/robert-feil/ (last visited Jan. 9, 2019); *see also Previous and current research*, U. TÜBINGEN, https://uni-tuebingen.de/fakultaeten/mathematisch-naturwissenschaftliche-fakultaet/fachbereiche/interfakultaere-institute-und-zentren/ifib/arbeitsgruppen/gruppen-a-f/feil/research/ (last visited Jan. 9, 2019).

mechanisms by which PDE5A inhibition via sildenafil brings about an increased risk of melanoma. It identifies a growth-promoting connection between cGMP and the MAPK pathway in melanoma cells. Dhayade 2016 explains:

> (1) melanoma cells express a cGMP signaling pathway involving PDE5;
>
> (2) this cGMP pathway promotes MAPK signaling and melanoma cell growth and migration;
>
> (3) PDE5, uninhibited, degrades cGMP and thus normally acts as a brake on this growth-promoting cGMP pathway in melanoma; and
>
> (4) PDE5 inhibitor drugs release the PDE5 brake, leading to increased tumor growth.

*See id.*

First, Dhayade 2016 shows that melanoma cells express PDE5, as previously shown in Arozarena 2011 and other studies, further demonstrating that PDE5 inhibitors can plausibly impact melanoma cells via PDE5. Second, the study demonstrates a cGMP pathway impacting melanoma cell growth via MAPK signaling. The authors note that "cGMP has been implicated in the regulation of growth and survival in multiple cell types including tumor cells (Fajardo 2014; Feil 2003; Feil 2005)." *Id.* at 2600. They further explain:

> The role of cGMP in cancer appears to be complex and dependent upon the type of tumor and model system under investigation (Barsoum 2014; Fajardo 2014; Ying & Hofseth 2007; Zhange 2014). Both pro- and anti-cancer effects of cGMP have been reported. The variable effects of cGMP on tumor growth are likely due to the fact that different tumor cells express different cGMP generators and effectors and that cGMP signaling also affects various processes in the tumor microenvironment, such as blood flow, angiogenesis, inflammation, and immune response.
>
> The aim of the present study was to characterize the expression and functional role of components of the cGMP signaling system in melanoma cells of murine and human origin. We have identified a cGMP pathway that promotes MAPK signaling and melanoma growth in vitro and in vivo. Importantly, it was found that the growth-promoting cGMP pathway could be potentiated pharmacologically by treatment of melanoma cells or mice with sildenafil.

*Id.*[15]

[15] Again, the MAPK pathway (also known as the MEK, ERK, or RAS/RAF/MEK pathway) is hyper-activated in the majority of melanomas. JX 87, Dhayade 2016 at 2599. Activation of the MAPK pathway typically occurs through NRAS or BRAF mutations (55% to 70% of cutaneous melanomas). *Id.*

Third, the study analyzes PDE5's impact on the cGMP-MAPK pathway. The study explains that because PDE5 normally degrades (i.e. decreases) cGMP, it acts as a brake on the growth-promoting cGMP pathway in melanoma cells. The authors show that "pharmacological experiments with PDE5 inhibitors (sildenafil, tadalafil, and vardenafil) demonstrated that PDE5 [uninhibited] contributes to the degradation of cGMP and is, thus, an important 'brake' for cGMP signaling in melanoma cells." *Id.* at 2604.

Finally, the authors demonstrate that PDE5 inhibitors, through their effect of increasing cGMP by blocking its normal degradation, enhance the activity of MAPK via cGKI—leading to increased melanoma progression. *Id.* at 2605.

Dhayade 2016 builds on Arozarena 2011 further elucidating plausible mechanisms by which sildenafil and tadalafil bring about increased melanoma progression. Although their studies reveal similar yet different plausible mechanisms, Dhayade 2016 explains how both mechanisms can work together in a cyclical, self-reinforcing loop of enhanced melanoma progression involving PDE5 inhibition:

> Our results with sildenafil are in agreement with a recent study that indicated a link between PDE5 and cGMP signaling in melanoma. [Arozarena 2011] reported that in melanoma cells oncogenic BRAF, acting through MEK and the transcription factor BRN2, downregulates PDE5 expression. PDE5 downregulation was associated with a relatively modest increase in cGMP and cytosolic $Ca^{2+}$ and promoted the invasiveness of melanoma cells. However, the effect of sildenafil on the growth of primary tumors was not determined in this study, and the potential cGMP generators and effectors were not identified. Thus, while [Arozarena 2011] describe[s] an influence of MAPK on cGMP signaling, in that enhanced MAPK activity results in increased cGMP levels via downregulation of PDE5, our study reports vice versa that cGMP also impacts MAPK signaling, in that increased levels of cGMP enhance the activity of MAPK via cGKI. […]
>
> Based on the present study and previous findings (Arozarena 2011; Schonrath 2011), we suggest a model in which a bidirectional crosstalk of cGMP and MAPK signaling promotes the switch of non-metastatic cells in primary melanomas to invasive/metastatic cells. [Figure S5 …]
>
> Our data together with the findings of [Arozarena 2011] raise concerns that use of sildenafil (Viagra) or other PDE5 inhibitors like vardenafil (Levitra) or tadalafil (Cialis) could promote melanoma in humans.

*Id.* at 2604-2606; *see also id.* at Figure S5:

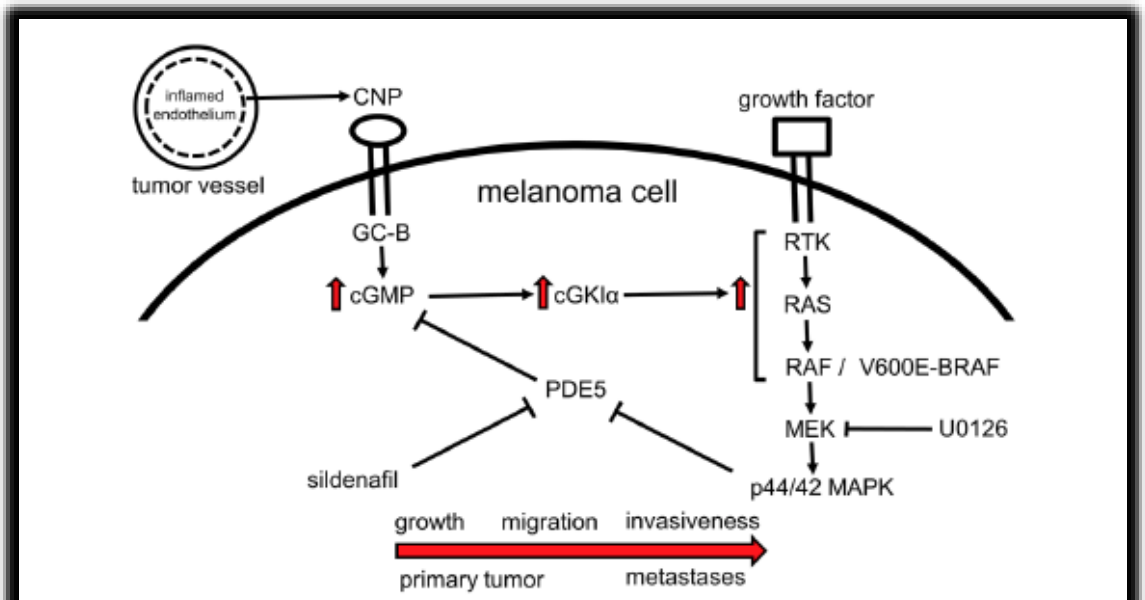


**Figure S5 (Related to Figure 7). Model of cGMP Signaling in Melanoma Pathogenesis**

The scheme illustrates how a bidirectional crosstalk of cGMP and MAPK signaling promotes the switch of non-metastatic cells in primary melanomas to invasive/metastatic cells. CNP is released from endothelial cells (dashed circle) of the inflamed tumor vasculature (upper left) and binds to its receptor, GC-B, on melanoma cells. Thereby, CNP triggers an increase of the intracellular cGMP concentration and activation of cGKIα in the melanoma cells. Via phosphorylation of yet unknown substrate proteins, cGKIα promotes MAPK signaling upstream of MEK (indicated by the bracket), resulting in cells with increased potential for growth, migration, and invasiveness to develop. Degradation of cGMP via PDE5 acts as a "break" in this switching process. However, a persistent increase in MAPK signaling, for instance, by sustained activity of the CNP-cGMP-cGKI cascade and/or by somatic gain-of-function mutation of BRAF to V600E-BRAF (Arozarena et al., 2011), results in downregulation of PDE5 at the transcriptional level. This releases the PDE5 "break", thus, establishing a feed-forward, self-reinforcing loop that further enhances the aggressiveness of the melanoma cells. The PDE5 "break" can also be released pharmacologically by the PDE5 inhibitor sildenafil. Note that CNP and sildenafil might act mainly on cells of the primary tumor to increase their metastatic potential, and that "switched" metastatic cells might lose expression of both cGKI and PDE5. Note also that the present study has analyzed the effects of exogenously supplied CNP. The role of inflamed tumor vessels as the source of endogenous CNP in melanomas needs to be established in future studies. U0126 is a MEK inhibitor used in the present study. RTK stands for receptor tyrosine kinase.

### D. There is Widespread Acceptance of the Biological Mechanism by which Sildenafil and Tadalafil Can Cause the Development of Melanoma Cancer.

Prior to litigation, Defendants Pfizer and Eli Lilly separately conducted their own internal evaluations of relevant mechanistic data and both concluded there was supportive evidence of biological plausibility. [redacted]

[redacted]

[redacted][16]

Further, a number of additional peer-reviewed scientific studies, review articles, and analyses support or acknowledge the biological plausibility of the mechanism by which PDE5 inhibitors such as sildenafil and tadalafil bring about melanoma progression. As Dhayade 2016 notes "[t]he link between sildenafil and melanoma development is further supported by the finding that PDE5 inhibitors promote melanin synthesis, which may exacerbate melanoma development." JX 87 at 2607 (citing JX 118, Zhang *et al., PDE5 Inhibitor Promotes Melanin Synthesis Through the PKG Pathway in B16 Melanoma Cells*, 113 J. CELLULAR BIOCHEMISTRY 2738 (2012); JX 114, Noonan *et al., Melanoma Induction by Ultraviolet A but not Ultraviolet B Radiation Requires Melanin Pigment*, 3 NAT. COMMUN. 884 (2012)). Schonrath 2011 demonstrated that increased cGMP levels enhanced migration capacity of skin cancer cells. PX 16, Schonrath *et al., Involvement of VILIP-1 & Opposite Roles of Cyclic AMP & GMP Signaling in In Vitro Cell Migration of Murine Skin Squamous Cell Carcinoma*, 50 MOLECULAR CARCINOGENESIS 319 (2011). Also, germline mutations affecting PDE5A are a risk factor for melanoma, consistent with the proposition that PDE5 plays a role in melanoma pathogenesis. PX 17, Fidalgo *et al., Role of Rare Germline Copy Number Variation in Melanoma-Prone Patients*, 12 FUTURE ONCOLOGY 1345 (2016).

Peer-reviewed scientific literature concludes, sometimes explicitly, that melanoma progression via PDE5 inhibitor use is biologically plausible.

> Given that PDE5A down-regulation increased invasiveness and that PDE5A expression was higher in primary tumors than in metastatic tumors, **it is biologically plausible that PDE5A inhibitors may promote invasion of primary tumors**. The previous study tested melanoma cell lines mostly of metastatic origin and did not test invasive potential of cells

[16] [redacted]

> from primary tumors. However, because primary tumors expressed substantially higher levels of PDE5A than did metastatic melanomas, the effect may be more marked. Melanoma is highly heterogeneous in its characteristics, unlike cell lines, so even a small population of cells that respond strongly could be significant.

JX 90, Li 2014 (emphasis added) (referencing JX 85, Arozarena 2011 and PX 18, Hoek *et al.*, *In Vivo Switching of Human Melanoma Cells Between Proliferative & Invasive States*, 68 CANCER RES. 650 (2008)).

> Phosphodiesterase type 5 (PDE5), the target of oral erectile dysfunction drugs, is part of the RAS-RAF-MEK-ERK signaling pathway that has been implicated in the development of malignant melanoma. Specifically, mutations in the *BRAF* gene lead to down-regulation of PDE5, which increases cytosolic calcium via cyclic guanosine monophosphate, which ultimately increases the invasiveness of melanoma cells. This has raised questions regarding whether PDE5 inhibitors used to treat erectile dysfunction promote malignant melanoma through a similar mechanism.

JX 93, Loeb 2015 at 2450.

> **There is some biological evidence that the use of PDE5-Is may increase the risk of melanoma skin cancer**. First, PDE5 is widely expressed in many tissues, including melanocytes. Second, it is well established that activating mutations of the oncogene BRAF are common in melanoma skin cancer. Although some preclinical studies have raised the possibility that PDE5 inhibition might have therapeutic value in cancer treatment, Arozarena *et al.* showed that one consequence of BRAF activation is suppression of expression of PDE5A, the gene that encodes PDE5, and that this leads to increased invasiveness. **Consequently, pharmacologic inhibition of PDE5A could simulate the effect of BRAF activation on this target gene.**

JX 91, Lian 2016 (emphasis added).

> Laboratory evidence suggests that **reduced PDE5 expression** triggered by BRAF activation **increases the invasiveness and metastatic potential of melanoma cells**; hence, pharmacological inhibition of PDE5 might have an unintended effect on melanoma risk. In addition, PDE5 inhibitors appear to promote melanin synthesis, which in turn can significantly facilitate the development of melanoma

JX 94, Matthews 2016 (emphasis added) (citing JX 85, Arozarena 2011; JX 118, Zhang 2012; and JX 114, Noonan 2012).

> **An increased melanoma risk associated with PDEI use is biologically plausible**. During the recent decade, knowledge of melanoma pathogenesis has improved, revealing that over 50% of melanomas contain activating mutations in BRAF (OMIM *164757) [Gray-Schopfer 2007; Bollag 2012; Hauschild 2012]. The downstream effect of BRAF activation is suppression of PDE5A, and the suppression of PDE5A stimulates melanoma cell invasion and metastasis [Arozarena 2011]. It is thus plausible that direct pharmacological inhibition of PDE5A may increase the risk of developing melanoma [Arozarena 2011].

JX 96, Pottegård 2016 (emphasis added).

> Phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil, tadalafil, and vardenafil inhibit cyclic guanosine-39, 59-monophosphate (cGMP)-degrading PDE5 in the vascular smooth muscle and are widely used treat erectile dysfunction. Interestingly, activation of this cGMP pathway has been shown to promote melanoma cell growth and migration, and this link has recently been confirmed.

JX 98, Tang 2017.

> Taken together, our findings in human melanoma cells and mice provide a plausible mechanistic explanation for a causal relationship between sildenafil and melanoma in men. Based on our results we assume that sildenafil, and possibly other PDE5 inhibitors, could first and foremost promote the growth/malignancy of existing melanomas. Thus, possible adverse effects of PDE5 inhibitors should be considered in patients with melanoma, particularly if they use these medications frequently and in high dosages, for instance to treat pulmonary hypertension.

JX 104, Feil, *Viagra Releases the Brakes on Melanoma Growth*, 4 MOLECULAR & CELLULAR ONCOLOGY, e1188874 at 3 (2017).[17]

**E. Studies which Demonstrate Sildenafil and Tadalafil Can Cause the Development of Melanoma Cancer Do Not Conflict with Studies of Purported Anti-Cancer Effects of PDE5 Inhibitors.**

Defendants' experts assert that anti-cancer research involving PDE5 inhibitors is highly relevant to this litigation; however, this is merely a red herring. PDE5 inhibitors have been studied for potential anti-cancer effects in two categories: (1) a direct anti-cancer effect in which PDE5 inhibitors are examined for impact on the tumor itself, and (2) an indirect anti-cancer effect related to PDE5 inhibitors' impact on the immune system. Although Plaintiffs' experts considered this research in forming their opinions, studies relating to these anti-cancer theories do not negate the established scientific evidence supporting the mechanism of action by which PDE5 inhibitors sildenafil and tadalafil cause the progression of melanoma.

[17] *See also* the FDA's assessment regarding biological plausibility. On August 19, 2016, the FDA's Office of Pharmacovigilance and Epidemiology published a review of PDE5-inhibitor use and the increased risk of melanoma: "We acknowledge there may be a biologically plausible mechanism for PDE5 inhibitors and melanoma." PX 19, FDA00000001 at 11.

As an initial matter, experts for both Defendants mistakenly equate the results of studies examining PDE5 inhibitors and other non-melanoma cancers to melanoma by using methodology that is inherently flawed. Melanoma, as explained above, is a cancer of the melanocytes. Melanocytes are derived from neural crest cells formed during embryonic development. In contrast, many other cancers are derived from different cell types, such as colon cancer which is derived from epithelial cells. As a consequence, different cancer types behave and respond differently—for example, chemotherapy treatments and drugs designed to inhibit certain cancer mutations do not elicit the same result in all cancer types. *See, e.g.,* JX 85 at 49-50 (Arozarena 2011 demonstrated PDE5 regulation differences between melanoma and colorectal cells). Even Defendants' experts agree that melanoma is a distinctly different type of cancer and that a drug or compound can have differing effects based on the type of cancer.[18] Thus, the results of anti-cancer studies involving other cancer types cannot be extrapolated and applied to melanoma, and should be excluded from the opinions of Defendants' experts.[19] Many of the studies Defendants' experts rely on concerning direct and indirect potential anti-cancer effects fall into this category.

[18] JX 83, Cohen Dep. at 241-42; JX 69, Schuchter Dep. at 221-24.

[19] *See, e.g.,* PX 20, Califano, *et al. Tadalafil Augments Tumor Specific Immunity in Patients with Head and Neck Squamous Cell Carcinoma*, 21 CLINICAL CANCER RES. 30 (2015) (head and neck squamous cell carcinoma); PX 21, Weed *et al., Tadalafil Reduces Myeloid-Derived Suppressor Cells and Regulatory T Cells and Promotes Tumor Immunity in Patients with Head and Neck Squamous Cell Carcinoma*, 21 CLINICAL CANCER RES. 39 (2015) (head and neck squamous cell carcinoma); PX 22, Mei *et al., Sildenafil inhibits the growth of human colorectal cancer in vitro and in vivo*, 5 AM. J. CANCER RES. 3311 (2015) (colorectal cancer); PX 23, Sarfati *et al., Sildenafil and vardenafil, types 5 and 6 phosphodiesterase inhibitors, induce caspase-dependent apoptosis of B-chronic lymphocytic leukemia cells*, 101 BLOOD 265 (2003) (B-chronic lymphocytic leukemia cells); PX 24; Sharman *et al., Cyclic-GMP-Elevating Agents Suppress Polyposis in Apc$^{Min}$ Mice by Targeting the Preneoplastic Epithelium*, 11 CANCER PREV. RES. 81 (2018) (preneoplastic intestinal epithelium); PX 25, Sponziello *et al., PDE5 expression in human thyroid tumors and effects of PDE5 inhibitors on growth and migration of cancer cells*, 50 ENDOCRINE 434 (2015) (papillary thyroid carcinoma); PX 26, Tuttle *et al., The cyclic GMP/protein kinase G pathway as a therapeutic target in head and neck squamous cell carcinoma*, 28 CANCER LETTERS 279 (2015) (head and neck squamous cell carcinoma); PX 27, Islam *et al., Sildenafil Suppresses Inflammation-Driven Colorectal Cancer in Mice*, 10 CANCER PREV. RES. 377 (2017) (colorectal cancer); PX 28, Lin *et al., Phosphodiesterase-5 inhibition suppresses colonic inflammation-induced tumorigenesis via blocking the recruitment of MDSC*, 7 AM. J. CANCER Res. 41 (2017) (colon epithelial cells); PX 29, Capuano *et al., Modulators of arginine metabolism support cancer immunosurveillance*, 10 BMC IMMUNOLOGY 1 (2009) (colon carcinoma); PX 30, Karakhanova *et al., Characterization of myeloid leukocytes and soluble mediators in pancreatic cancer: importance of myeloid-derived suppressor cells*, 4 ONCOLMMUNOLOGY e998519 (2015) (pancreatic cancer).

Two examples highlighting this distinction are Califano 2015 and Weed 2015—clinical trials that deal exclusively with potential effects of PDE5 inhibitors on head and neck squamous cell carcinoma. PX 20, PX 21. Many of Defendants' experts cite to these two studies to bolster their argument that PDE5 inhibitors might have anti-cancer effects in melanoma, but for the reasons already described, this comparison is scientifically unfounded. Pfizer expert Dr. Califano was an author on both of these studies, and even admitted in his deposition that his research had not established any anti-cancer effects with respect to melanoma.[20] The difference in any potential effect with respect to melanoma is further supported by the list of ongoing clinical trials testing potential anti-cancer effects of PDE5 inhibitors found in Pantziarka 2018 and cited by several of Defendants' experts. PX 31, Pantziarka *et al., Repurposing drugs in oncology (ReDO)-selective PDE5 inhibitors as anti-cancer agents*, 12 ECANCERMEDICALSCIENCE 824 (2018). This review article cites to eleven (11) ongoing trials; however, none are focused primarily on melanoma. *Id.* These examples strongly support that mainstream science recognizes that the same substance may have differing impacts depending on the type of cancer tested; thus, research related to one specific cancer type has little bearing on a different cancer type.

Defendants' experts also rely on studies involving PDE inhibitors with inherently different pharmacodynamic and pharmacokinetic properties to support their direct anti-cancer effect theories. Sildenafil and tadalafil are PDE5 inhibitors which inhibit PDE5 selectively at low concentrations ("high potency") at which other PDE isozymes are not also inhibited ("high selectivity"). Defendants' experts attempt to extrapolate the results of studies examining very different, less selective and less potent inhibitors of PDE5. *Compare* JX 100, Bischoff, E., *Potency, selectivity, and consequences of nonselectivity of PDE inhibition*, 16 INT'L J. IMPOTENCE RES. S11, S13 (2004). (Table 2) *with* PX 32, Whitt *et al., Sulindac sulfide selectively increases sensitivity of ABCC1 expressing tumor cells to doxorubicin and glutathione depletion*, 30 J. BIOMEDICAL RES. 120, 129 (2016) (Table 1) (The highly

[20] JX 67, Califano Dep. at 141 ("Q: Okay. Do you believe – is .it your opinion, Doctor, that Viagra is associated with an anti-tumor effect in melanoma? A: I don't have an answer to that question. Q: You don't have an opinion on whether or not it is or not? A: I don't – I don't – I don't have – Well, in – in certain experimental systems, potentially, yes. But as to whether it's effective anti-cancer effect in human melanoma, I don't have an answer to that.").

selective PDE5 inhibitor sildenafil inhibits PDE5 at a concentration ($IC_{50}$ value) of 8.5 nM/L whereas the non-selective PDE inhibitor sulindac sulfide only inhibits PDE5 at a concentration of 38,000 nM/L). Defense experts' comparison is misplaced—less potent and less selective inhibitors of PDE5 can have substantial off-target effects. These types of compounds inhibit multiple PDE isozymes[21] resulting in significant biological effects that cannot be attributed to the selective and potent PDE5 inhibitors sildenafil and tadalafil. Studies examining the effects of less selective and less potent PDE5 inhibitors (*i.e.*, sulindac, dipyridamole, and zaprinast) on melanoma have no bearing on the effect of sildenafil and tadalafil on melanoma. *E.g.*, JX 112, Murata 2010 (zaprinast, dipyridamole); PX 10, Drees 1993 (zaprinast); PX 32, Whitt 2016 (sulindac sulfide).

One such study, Murata 2010, tests the effects of less selective, less potent PDE inhibitors dipyridamole and zaprinast on melanoma. JX 112. One way to measure the effects of a drug on a molecule is by the $IC_{50}$ value. Essentially, the lower the $IC_{50}$ value, the more potent the drug is at inhibiting the target. When using a more potent drug, less of it is needed to inhibit the target. Zaprinast has an $IC_{50}$ value of **760** nM for PDE5 while dipyridamole has an $IC_{50}$ value of **900** nM. PX 33, Rascón *et al., Cloning and characterization of a cAMP-specific phosphodiesterase (TbPDE2B) from Trypanosoma brucei*, 99 PROC. NAT'L ACAD. SCI. U.S. 4714, 4718 (2002) (Table 1). In contrast, sildenafil and tadalafil have an $IC_{50}$ value for PDE5 of **8.5** nM and **9.4** nM, respectively. JX 100, Bischoff 2004. Further, sildenafil and tadalafil are far more selective for PDE5 over other PDE isozymes compared to zaprinast and dipyridamole. *See, e.g.*, PX 33, Rascón 2002, JX 100, Bischoff 2004. Although both zaprinast and dipyridamole have been characterized as PDE5 inhibitors, they are actually more selective for PDE6 than PDE5. Additionally, both drugs inhibit multiple other PDE isozymes even at low concentrations. PX 33, Rascón 2002 at 4718 (Table 1). As such, the effects of these drugs cannot be extended to the effects of PDE5 inhibitors like sildenafil and tadalafil. This is even further demonstrated in Figure 3 of Murata 2010 where dipyridamole, which is less selective for PDE5 than zaprinast, shows a much higher degree of cell growth inhibition in melanoma suggesting that any growth inhibitory effects are not directly attributable to the inhibition of PDE5. JX 112 at 357, Figure 3.

[21] In fact, these drugs inhibit other PDE isozymes more so than PDE5, unlike sildenafil and tadalafil.

Additionally, Defendants' experts have touted potential beneficial effects of PDE5 inhibitors on the immune system's ability to fight off cancer cells—including melanoma—and have even compared them to current FDA approved immunotherapies in an attempt to bolster their argument. This comparison is improper and highly misleading for several reasons. First, as discussed above, Dr. Califano admitted in his deposition that there is no established anti-cancer effect with respect to human melanoma. JX 67, Califano Dep. 141:4-14. Further, the only potential effect suggested in the published literature—that PDE5 inhibitors may decrease levels of inflammation-driven immune suppressor cells in the microenvironment of an established tumor—is separate and distinct from any current FDA approved immunotherapies. *Compare* JX 116, Serafini *et al., Phosphodiesterase-5 inhibition augments endogenous antitumor immunity by reducing myeloid-derived suppressor cell function*, 203 J. OF EXPERIMENTAL MED. 2691 (2006) ("The elimination, functional inhibition, or differentiation of MDSCs in tumor-bearing hosts can restore C8+ T cell responsiveness") *with* PX 34, Palucka and Coussens, *The Basis of Oncoimmunology*, 164 CELL 1233 (2016) (describing "passive" immunotherapies such as adoptive transfer of cytotoxic T cells and "active" immunotherapies such as immune checkpoint blockade as the two principal mechanisms of action of established cancer immunotherapies). Second, even the studies that investigate a potential anti-cancer effect do so when PDE5 inhibitors are administered as an **adjunct therapy—**that is, they are given with current standard of care treatments like chemotherapy or FDA approved immunotherapies. *See* JX 105, Hassel *et al., Tadalafil has biologic activity in human melanoma. Results of a pilot trial with Tadalafil in patients with metastatic Melanoma (TaMe)*, 6 ONCOIMMUNOLOGY e1326440 at 8 (2017) ("tadalafil seems to have a limited efficacy as a monotherapy" and "tadalafil could be combined with [FDA approved immunotherapies] and targeted treatments to potentially increase efficacy"); *see also* PX 20, Califano 2015 at 37. ("It should be noted that, to date, there are no studies showing any PDE5 inhibitor to have clinical anti-tumor activity as a single agent"). Such a situation is facially different from that faced by Plaintffs, who are taking PDE5 inhibitors for ED, PAH, or BPH, not for the purpose of cancer treatment. Perhaps most importantly, the published literature suggests that any potential anti-cancer effects are limited to later stages of primary tumor outgrowth. *See* JX 116, Serafini 2006 at 2692 ("The fact that no difference in tumor outgrowth was seen between early versus late administration of sildenafil suggests

that PDE5 inhibition does not appreciably affect the early phases of tumor uptake but rather influences the later stages of tumor outgrowth"). Effects on the late stages of primary tumor outgrowth take place after diagnoses of early stage cancer, at a later step of the metastatic cascade than the mechanism described by Arozarena 2011 and Dhayade 2016. *See* PX 41, Fidler, *The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited*, 3 NAT. REV. CANCER 453 (2003).

For all these reasons, this particular defense created argument is unreliable and has no bearing on whether PDE5 inhibitors can cause progression of melanoma. For over 20 years, Defendants and others have tried and failed to find indications for PDE5 inhibitors as anti-cancer drugs. Respectfully, this Court should not approve such a spurious indication in this forum, especially relating to melanoma.

## ARGUMENT

Plaintiffs below set forth a discussion of the Ninth Circuit Law on the admissibility of expert testimony, and then address individual Defendants' expert whose testimony should be excluded in whole or in part.

### I. THE NINTH CIRCUIT STANDARDS ON GENERAL CAUSATION AND EXPERT TESTIMONY.

#### A. General Causation.

Causation in pharmaceutical personal injury cases "is typically discussed in terms of generic and specific causation." *In re Hanford Nuclear Reservation Lit.*, 292 F.3d 1124, 1133 (9th Cir. 2002); *see also Bextra & Celebrex*, 524 F. Supp. 2d at 1171-72. General or generic causation refers to whether a drug has "the capacity to cause the harm alleged." *Id.* Specific causation refers to whether a drug caused the injury in a particular individual. *Id.*; *see also Roundup*, 2018 U.S. Dist. LEXIS 114760, at *77-78. Specific and general causation are two distinct questions and the analysis of expert testimony for each question is unique. The issue on the present motion is only general causation—whether or not there is a causal relationship between use of PDE5 inhibitors and melanoma progression.

**B. Admissibility of Expert Testimony**.

The district court acts as a "gatekeeper" before an expert may testify at trial, screening potential testimony under the standards set forth in FED. R. EVID. 702 and *Daubert*, 509 U.S. 579. Expert opinion testimony is admissible if:

(1) The witness is qualified by knowledge, skill, experience, training or education to testify about the subject she intends to address;

(2) The expert's specialized knowledge will help the jury understand the evidence or to determine a fact in issue;

(3) The testimony is based on sufficient facts or data;

(4) The testimony is the product of reliable principles and methods; and

(5) The expert has reliably applied the principles and methods to the facts of the case.

FED. R. EVID. 702; *see Roundup*, 2018 U.S. Dist. LEXIS 114760, at *73-74. Each party bears the burden of establishing the admissibility of their experts' testimony. *See, e.g.*, *Rondor Music Int'l Inc. v. TVT Records LLC*, 2006 U.S. Dist. LEXIS 97118, 2006 WL 5105272, at *3 (C.D. Cal. Aug. 21, 2006) (excluding testimony where expert was unable to articulate a specific process or methodology by which she reached her conclusions); *see also Scott v. Chipotle Mexican Grill, Inc.*, 315 F.R.D. 33, 44 (S.D.N.Y. 2016) ("experts must meet *Daubert*'s threshold standards regarding the qualifications of the expert, sufficiency of the data, reliability of the methodology, and relevance of the testimony").

While "Rule 702 should be applied with a 'liberal thrust' favoring admission," it requires an expert's testimony to be relevant and reliable. *See, e.g.*, *Messic v. Novartis Pharms. Corp.*, 747 F.3d 1193, 1196 (9th Cir. 2014) (quoting *Daubert*, 509 U.S. at 588). This Motion concerns the latter.

Only qualified witnesses may provide expert opinion testimony. *See* FED. R. EVID. 702; *United States v. Cordoba*, 104 F.3d 225, 229 (9th Cir. 1997). But even the most qualified expert cannot offer an opinion on subject matter outside his or her area of expertise; rather, "the expert's opinion must be grounded in his or her personal 'knowledge, skill, experience, training or education.'" *In re Ford Tailgate Litig.*, 2015 U.S. Dist. LEXIS 159534, at *23 (N.D. Cal. Nov. 25, 2015) (quoting FED. R. EVID. 702); *see Mullins*, 178 F. Supp. 3d at 888; *see also United Energy Trading, LLC v. Pac. Gas & Elec. Co.*, 2018 U.S.

Dist. LEXIS 178076 (N.D. Cal. Oct. 16, 208) ("Expert opinion testimony is reliable if such knowledge has a 'basis in the knowledge and experience of [the relevant] discipline.'") (quoting *Daubert*, 509 U.S. at 590).

Rule 702's reliability bar is not concerned with an expert's ultimate conclusions but instead focuses on his reasoning. *Wendell v. GlaxoSmithKline LLC*, 858 F.3d 1227, 1232 (9th Cir. 2017) ("focus of the district court's analysis 'must be solely on principles and methodology, not on the conclusions that they generate'") (quoting *Daubert*, 509 U.S. at 595). To be reliable for Rule 702 purposes, an expert's reasoning—his principles and methodology—must be "grounded in the methods of science." *Id.* (quoting *Clausen v. M/V New Carissa*, 339 F. 3d 1049, 1056 (9th Cir. 2003)).

Courts may consider a variety of factors in determining whether an expert's testimony is reliable, including whether: (1) the expert's theory or technique can be tested; (2) it has been subjected to peer review and publication; (3) the known or potential error rate of the theory or technique is acceptable; and (4) the theory or technique is generally accepted within the relevant scientific community. *See Messic*, 747 F.3d at 1197; *Wendell*, 858 F.3d at 1232. A court may also consider whether experts are "testifying 'about matters growing naturally' out of their own independent research, or if 'they have developed their opinions expressly for purposes of testifying.'" *Wendell*, 858 F.3d at 1232. No one of these factors is a threshold requirement, nor is the set of factors a threshold test that must be applied in every case, to every expert. *Id.*; *see also Roundup*, 2018 U.S. Dist. LEXIS 114760, at *76 ("factors are not a mandatory or inflexible checklist, and the Court has broad discretion to determine which factors are most informative in assessing reliability in the context of a given case."). Ultimately, the "factors are illustrative, and they are not applicable in each case." *Wendell*, 858 F.3d at 1232.

Consistent with Rule 702's focus on reasoning, the above factors should focus not on *what* the experts concluded but on *how* they reached their conclusions. *Id*; *see also Messic*, 747 F.3d at 1197. Each of the experts discussed below fail to meet one or more of Rule 702's reliability standards.

## II. DR. JOSEPH CALIFANO (EXPERT FOR DEFENDANT PFIZER).

### A. Dr. Califano Is Unqualified to Offer Testimony on Epidemiological Studies.

Dr. Califano is a physician who specializes in otolaryngology and surgical oncology.[22] JX 67, Califano Dep. at 12:10-13. He lacks the necessary qualifications to offer testimony relevant to the epidemiological studies at issue before this Court. He is not a trained epidemiologist, nor has he received formal education in epidemiology. *Id.* at 96:8-14 (he had taken "some" epidemiology courses but has not received a degree). As a result, his analysis of the observational studies and meta-analyses at issue is cursory at best—no more worthwhile than the opinions of a lay witness with an undeveloped understanding of epidemiology. Indeed, "Even the most qualified expert may not offer any opinion on any subject…" *Mullins*, 178 F. Supp. 3d at 900. Dr. Califano does not possess the knowledge or expertise in epidemiology required to offer his opinion to the trier of fact. As such, his testimony must be excluded.

### B. Dr. Califano Did Not Employ a Reliable Methodology to Support His Testimony.

Dr. Califano's lack of qualification is further reflected by his failure to use reliable methodology to analyze the epidemiological studies at issue. Copying the studies' findings directly into his report, Dr. Califano then summarily concluded that the studies, taken together, "do not support the conclusion that there is a causal relationship between PDE5 inhibitors and melanoma progression." JX 24, Califano Rpt. at 20. Nowhere in his report does Dr. Califano demonstrate how he came to his conclusion, through evaluation of the studies' results or otherwise. Unsurprisingly, as discussed in detail below, Dr. Califano admitted to his superficial review of the studies and expert material.

Admissibility of an expert's testimony requires more than blind reliance on his word alone. *Gen. Elec., Co. v. Joiner*, 522 U.S. 136, 146 (1997) ("[N]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert."). As such, an expert must be able to demonstrate that he employed a scientifically valid and reliable methodology to form the basis of his opinion. This is only more crucial for a witness like Dr. Califano, whom already lacks the necessary knowledge and expertise in melanoma epidemiology.

[22] *Joseph A. Califano, III, MD*, UC SAN DIEGO HEALTH, https://providers.ucsd.edu/details/32523/joseph-califano_iii-cancer-ent_head_and_neck_otolaryngology-surgery-la_jolla (last visited Jan. 10, 2019).

While Dr. Califano's report recites four of the nine Bradford-Hill criteria,[23] not once did he actually use those factors to analyze causation. *See id.* Even if he had, Dr. Califano's selective reference to only four factors utilized by epidemiologists sets forth an incomplete, invalid, and unreliable methodology.

Dr. Califano's failure to actually perform a Bradford-Hill analysis is manifest in his failure to acknowledge even one of the four factors he—improperly—handpicked. For instance, Dr. Califano admitted repeatedly that most of the observational studies found an association between melanoma and PDE5 inhibitors, with some resulting in statistical significance. JX 67, Califano Dep. at 49:16-22, 62:3-15, 85:18-24, 91:24-92:6, 108:8-12, 109:11-15, 123:14-19, 127:2-9. Nevertheless, nowhere in Dr. Califano's report is an analysis of the strength of those observed associations, one of his four principles to determine causation. Lacking even an incomplete analysis from cherry-picked Bradford-Hill factors, Dr. Califano's report apparently derives purely from his intuition. *See In re Accutane Litig.*, 191 A.3d 560, 592 (N.J. 2018) ("Results-driven analysis, or cherry-picking, undermines principles of the scientific method and is a quintessential example of applying methodologies (valid or otherwise) in an unreliable fashion."); *see also Zenith Elecs. Corp. v. WH-TV Broad. Corp.*, 395 F.3d 416, 418 (7th Cir. 2005). Barring further explanation, his results-driven determination that a causal relationship does not exist between PDE5 inhibitors and melanoma progression is just conjecture and not admissible under Rule 702.

The Court need not take Plaintiffs' word for the fact that Dr. Califano's "analysis" is incomplete; he admitted it himself and could not explain why he referenced only a partial methodology:

> Q: This kind of test for causation that you have here is what you use on a day-to-day basis; is that right?
>
> A: Yes. These are ***some*** of the main things we use to look in taking into account whether or not association is related to causation.
>
> Q: Okay. But this is just from your experience; it doesn't come from a publication or some other authority?
>
> A: So there's multiple publications that write on this topic.
>
> Q: Okay. I just couldn't find one that had these specific variables. So I was trying to figure out if there was a certain place you had gotten this.

[23] According to Dr. Califano, the Bradford-Hill criteria "is a set of criteria [used as] a way of looking to see if the strength of data indicate towards causality." JX 67, Califano Dep. at 48:22-24.

A: Not that I recall.

JX 67, Califano Dep. at 47:19 to 48:12 (emphasis added).

Dr. Califano's selective reference to *some* criteria undermines the reliability of his conclusion denying a causal link between PDE5 inhibitors and the development of melanoma. *See Orrell v. AstroZeneca Pharm, LP (In re Nexium Esomeprazole)*, 662 Fed. App'x 528 (9th Cir. 2016) (excluding general causation testimony of expert who employed an "extremely thin" Bradford-Hill analysis). Although each of the nine Bradford-Hill criteria need not be satisfied in order to reach a reliable causation opinion, a selective analysis of some criteria is not proper. *See* JX 102, Hill 1965 at 299 ("None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*."); *Orrell*, 662 Fed. Appx. at 530; *Milward v. Acuity Specialty Prods. Grp., Inc.*, 639 F.3d 11, 26 (1st Cir. 2011); *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 466, 480-81 (E.D. Pa. 2014) (holding that since "the experts did not adequately consider the Bradford-Hill criteria as a whole, [their] causal conclusions were not formed using a reliable scientific method."). *Accord In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 796 (3d Cir. 2017); *Magistrini*, 180 F. Supp. 2d at 607; *Milward v. Acuity Specialty Prods. Grp., Inc.*, 639 F.3d 11, 26 (1st Cir. 2011) (quoting *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999)). Dr. Califano's causal conclusions must be excluded.

Actual analysis is imperative in analyzing epidemiology, as an epidemiological study, by itself, does not test for causation. *See Roundup*, 2018 U.S. Dist. LEXIS 114760, at *85-86 ("Whether that agent causes the outcome, however, cannot be proven by epidemiological studies alone; an evaluation of causation requires epidemiologists to exercise judgment about the import of those studies and to consider them in context."). *Accord* PX 37, *RMSE* at 23 (studies "when considered separately, cannot prove general causation"). Dr. Califano conceded as much in his deposition. JX 67, Califano Dep. at 44:25-45:5. His failure to do so all the more demonstrates his opinions' unreliability and inadmissibility under Rule 702.

### C. Dr. Califano's Unsupported Testimony on Biological Plausibility Does Not Assist the Trier of Fact.

Dr. Califano's conclusion that there is a lack of biological plausibility is unsupported. Testimony based on unsupported evidence would only serve to mislead, rather than assist, a trier of fact. *Best v. Lowe's Home Ctrs., Inc.*, 563 F.3d 171, 176-77 (6th Cir. 2009); *see* FED. R. EVID. 702. Thus, exclusion is warranted where an expert ignores highly relevant evidence that would negatively impact his conclusions. *See In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig.*, 2018 U.S. Dist. LEXIS 182420, at *119-121 (S.D.N.Y. 2018); *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 796-800 (3d Cir. 2017). Dr. Califano's preconceived bias that PDE5 inhibitors might have an anti-cancer therapeutic effect improperly precluded him from rendering a reliable opinion on the biological plausibility of the drugs' effect on melanoma progression.

Dr. Califano summarily rejected the idea that there is a biologically plausible mechanism by which the drugs can affect melanoma progression, listing studies examining potential anti-cancer effects of PDE5 inhibitors on other forms of cancer. JX 67, Califano Dep. at 98:2 to 99:17. "[I]t is crucial that the expert supply his method for weighting the studies he has chosen to include in order to prevent a mere listing of studies and jumping to a conclusion." *Magistrini*, 180 F. Supp. 2d at 607; *Mirena*, 2018 U.S. Dist. LEXIS 182420, at *135; *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 796 (3d Cir. 2017). Importantly, the expert must be able to explain how his selection process was not merely "conclusion-oriented." *Magistrini*, 180 F. Supp. 2d at 603-607. Yet Dr. Califano's opinions on biological plausibility are conclusory—he does not believe there is a plausible link between PDE5 inhibitors and melanoma, yet he could not offer an explanation as to how he reconciled his opinion with conflicting data. *See* JX 67, Califano Dep. at 108:13-20.

In contrast to his litigation driven report, Dr. Califano agreed that an association had been demonstrated in at least one specific melanoma cell line, thereby indicating that PDE5 inhibitors could potentially increase the invasion of melanoma cells. *Id*. at 100:13-19. Additionally, he rejected the premise that PDE5 inhibitors could cause melanoma invasion in mice, yet conceded that there was data demonstrating melanoma growth in a specific mouse model. *See id*. at 100:25 to 101:5, 126:12-20.

Likewise, Dr. Califano rejected Arozarena 2011 and Dhayade 2016 for their collective failure to provide a consistent theory regarding growth and invasion of melanoma cells, *id.* at 99:10-13, yet he admitted that data within the studies suggested a link between PDE5 inhibitor use and melanoma progression, *id.* at 100:13-19, 100:25 to 101:1-5, 126:12-20. Specifically, he agreed that data existed that demonstrated sildenafil use potentiated melanoma growth in a mouse model, *id.* at 104:5-21, and that PDE5 inhibitors were shown to increase the invasion of melanoma cells, albeit in limited situations, *id.* at 104:23-25 to 105:1-2.

Despite the evidence demonstrating plausibility, which he acknowledged in his deposition, Dr. Califano selectively disregarded the data in favor of his own, litigation-driven conclusions. Dr. Califano specifically ignored evidence that contradicted his preconceived theories and failed to provide an analysis of how he arrived at his conclusions. His testimony on biological plausibility is patently unreliable and would only serve to mislead the trier of fact.

### D. Dr. Califano's Cursory and Selective Review of Materials Undermines His Opinions.

Finally, Dr. Califano's improper selective review of the massive amounts of materials he references demonstrates the litigation-driven and unreliable nature of his opinions. The total number of hours he supposedly spent working as an expert in this litigation is incredulously low when compared to the amount of documentation he allegedly reviewed. As of September 21, 2018, Dr. Califano spent approximately fifty hours of his time dedicated to this litigation. *Id.* at 11:6-10. Of that time, he spent approximately fifteen hours drafting his 33-page, single-spaced report, and an additional number of hours performing a literature search. *Id.* at 15:1-3, 16:21-23, 17:5-12. He allegedly read selected reports from Plaintiffs' experts, but could only remember four specifically. *Id.* at 18:11-24, 19:2-11, 20:9-14, 21:9-19, 22:9-14. He purportedly spent 20 hours reviewing 52 documents referenced in the footnotes of his expert report which total approximately 6,000 pages. *Id.* at 25:19-25, 26:1-7. Dr. Califano's testimony suggests his report was created in haste or by someone else, accounting for his failure to apply a valid methodology by which to render a reliable opinion.

Where a witness performs a cursory review of highly relevant data, such analysis falls below the standard of reliability expected of an expert. *Interwoven, Inc. v. Vertical Computer Sys.*, 2013 U.S. Dist. LEXIS 100790, at *21 (N.D. Cal. July 18, 2013); *see Kljajic v. Whirlpool Corp.*, 2017 U.S. Dist. LEXIS 70784, at *47-48 (N.D. Ill. May 9, 2017). Consequently, Dr. Califano's perfunctory review of the materials in this litigation renders his testimony unreliable.

As noted above, Dr. Califano was also inappropriately selective in the material he deemed relevant. *See* JX 67, Califano Dep. at 27:10-25. "Result-driven analysis, or cherry-picking, undermines principles of the scientific method and is a quintessential example of applying methodologies (valid or otherwise) in an unreliable fashion." *In re: Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prods. Liab. Litig. (No. II) MDL 2502*, 892 F.3d 624, 634 (4th Cir. 2018); *see also Accutane*, 191 A.3d at 592. For studies he read prior to this litigation, Dr. Califano chose to only review the abstracts. JX 67, Califano Dep. at 26:3-7. For studies he was unfamiliar with, they were not read "cover-to-cover" since information, such as the supplementary data results, were not considered important to his review. *Id.* at 26:22-25 to 27:1-6. Dr. Califano admitted he read only select excerpts and skimmed through Plaintiffs' experts' depositions. *Id.* at 19:2-11. He did not even recall reviewing Defendants' experts' reports, nor did he remember reviewing Dr. Piazza's supplemental expert report. *Id.* at 24:3-14, 24:14-19.

Despite his admission it was "certainly possible" that there were small areas he missed, Dr. Califano was confident his way of examining the data allowed him to reach "significant conclusions":

> Q: So are you absolutely certain that there was no relevant data or information in the portions that you didn't need—read that you needed for your report?
>
> A: Oh, it's certainly possible that there may be small areas or small, modest significant areas of data that I missed, perhaps, but . . .
>
> Q: You're just not sure?
>
> A: No. I think, as I said, because I spend most of my professional time examining these types of data, that I'm confident that the way in which I examined it actually allows me to reach significant conclusions, definitive conclusions about the data.

*Id.* at 28:3-15. He could not explain several oversights, such as his complete failure to consider the sildenafil-only results in the Loeb 2015 study (which showed a statistically significant association between melanoma and sildenafil use). *Id.* at 62:23 to 64:10. Dr. Califano's cherry-picking demonstrates a results-

driven approach that impinges the reliability of his testimony. Because his report failed to meet the requirements of admissibility, Dr. Califano's testimony must be excluded. *See Interwoven*, 2013 U.S. Dist. LEXIS 100790, at *21 (excluding the testimony of an expert who admitted he "didn't have to do much research [to form the basis of his opinion] because . . . it didn't seem necessary.").

## III. DR. RICHARD MARAIS (EXPERT FOR DEFENDANT PFIZER).

Dr. Marais is one of many authors listed on the Arozarena study. As to his "opinions" regarding his own research, Dr. Marais offered fact witness—not expert witness—testimony regarding the experiments conducted in his laboratory. He attempted to explain away the data and explicit conclusions as written in Arozarena 2011—statements published before he became a paid consultant for Pfizer.

First, Dr. Marais' overarching opinion as set forth in his report—and directly contrary to the statements in his peer-reviewed publication—was that his "research does **not** support the Plaintiffs' experts' theories, and there is no reliable evidence that sildenafil or other PDE5 inhibitors can cause melanoma progression." JX 27, Marias Rpt. at 1. To the extent that Dr. Marais offers purported expert testimony on biological plausibility based upon Arozarena 2011, Dr. Marais' purported expert testimony is improperly litigation-driven, as demonstrated by his own contrary words in his peer-reviewed publication.

Second, while Dr. Marais might have been qualified to offer opinions on whether or not there is a plausible biological mechanism of action by which PDE5 inhibitors may cause the growth and invasion of melanoma, his opinion is based on an improper standard and should be excluded.

Third, Dr. Marais purports to offer broader opinions, not adequately disclosed in his report, on epidemiology and on general causation. He does not have the necessary qualifications to testify on epidemiology and has not followed a proper methodology to offer an ultimate opinion on causation.

### A. Dr. Marais's Opinions on Biological Plausibility Are Inconsistent with His Prior Published Work, Litigation-Driven, and Unreliable.

Dr. Marais' opinions are litigation driven and counter to his own peer-reviewed, published research on PDE5 downregulation and melanoma cell invasion. "[T]he primary purpose of any *Daubert* inquiry is for the district court to determine whether that expert, 'whether basing testimony upon professional studies

or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.'" *McClain v. Metabolife Int'l, Inc.,* 401 F.3d 1233, 1237 (11th Cir. 2005) (internal citation omitted); *see also* FED. R. EVID. 702 advisory committee's notes (noting additional indicia of reliability including whether the expert was as careful with his litigation consulting as he or she would have been in his regular professional work). Litigation-driven opinions cannot withstand this level of *Daubert* scrutiny and should be excluded. *See Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1319-1320 (11th Cir. 1999). Federal courts have held that when an expert contradicts himself on an issue, his opinion is beyond the legal realm of permissible testimony. *See id.* at 1321 (expert's "about face" of opinion as to the cause of a patient's disease led the court to exclude opinion because it was obviously developed in anticipation of litigation); *see also Sloan Valve Co. v. Zurn Indus., Inc.*, 33 F. Supp. 3d 984, 1001 (N.D. Ill. 2014) (excluding expert opinion where expert's "own scholarship contradicts" his methodology).

Dr. Marais purports to offer expert opinions which are in reality factual testimony regarding the Arozarena 2011 study, on which he is listed as an author. Dr. Marias provided in his report a self-serving description of the other authors' motivations in conducting their study. *See, e.g.*, JX 27, Marais Rpt. at 28. In his deposition, he attempted to offer hearsay testimony of conversations with the first-named author, Dr. Arozarena, regarding the genesis of the study and the conduct of the experiments[24]. For example, although reported nowhere in the publication, Dr. Marais testified about conversations he had with Dr. Arozarena regarding the thought process of selecting the dosing of PDE5A inhibitors used during the mouse experiments, although this is an issue on which he has no personal knowledge and that he admits was not discussed in the publication itself. JX 71, Marais Dep. at 155-159.

Dr. Marais admitted that it was Dr. Arozarena that did the majority of the work reported in the publication. *Id.* at 123. Dr. Marais himself did not conduct the experiments reported in the publication—rather his role, as he described, was as follows:

> I was the group leader, the team leader, and therefore it was really my role to direct the science, to provide areas in which we were going to work, to provide the

[24] It appears that Pfizer hired Dr. Arozarena at one point as a consultant for the purposes of this litigation, but Dr. Arozarena was not disclosed as a testifying expert nor did he submit a report.

> strategic oversight of the laboratory and then, of course, to finance the research through grant applications.

*Id.* at 127.

This is uncorroborated factual testimony, not expert opinion. Nonetheless, to the extent that Dr. Marais does offer expert opinions regarding biological plausibility based on this publication, those opinions are unreliable. They are litigation-driven and at odds with the statements in the peer-reviewed study itself.

In his report, Dr. Marais opined that in Arozarena 2011, "we cautioned against interpreting our research to suggest that PDE5A inhibitors, such as sildenafil, cause the progression of melanoma." JX 27, Marais Rpt. at 3. In fact, the peer-reviewed study explicitly states the opposite, that "PDE5A regulates melanoma cell invasion." JX 85. In discussing the critical Figure 4, Arozarena 2011 states "Thus, we conclude that PDE5A blocks invasion in BRAF mutant melanoma cells, and therefore, when it is downregulated or inhibited, the cells invade." *Id.* at 49. In this experiment, inhibition of PDE5 was accomplished through treatment of the cells with sildenafil. Indeed Dr. Marais was forced to admit that the experiment as depicted does show melanoma invasion through "pharmacological inhibition" (that is, invasion from the application of sildenafil). JX 71, Marias Dep. at 141-142.

Arozarena 2011 ultimately determines: "Thus, we conclude that PDE5A is not a therapeutic target in melanoma, and our data even raise the possibility that PDE5A drugs could promote melanoma metastasis." JX 85 at 55. Dr. Marais at his deposition latched to the following sentence—"However, we do not perceive this to be a problem." But Arozarena 2011 goes on to tie this sentence to the fact that as of 2011 (when Arozarena was published), no observational studies had been published demonstrating an association between PDE5A inhibitors. It reads: "There are no reports linking these drugs to increased risk of melanoma metastasis, and we found that sildenafil did not increase mouse lung colonization in melanoma cells." *Id.* at 55. Of course, beginning in 2014 with the Li 2014 study, there developed a plethora of epidemiological studies showing associations between PDE5 inhibitor use and melanoma, as well as the Dhayade 2016 study which further demonstrated biologically plausible mechanisms in both in vitro and in vivo experiments.

Critically, Arozarena 2011 wraps up this discussion by concluding:

> Therefore, our data should be interpreted with care, and we do not immediately suggest that PDE5 inhibitors will drive melanoma metastasis. However, we caution that with the ever-widening clinical use of these drugs, **it is not possible to discount this risk completely**."

*Id.* at 55 (emphasis added).

Dr. Marais testified at his deposition that neither he nor any other author has retracted or published any correction of the statements in his paper. JX 71, Marais Dep. at 184-85. Nor has he made any effort to publically disagree with the plethora of published, peer-reviewed epidemiological papers that cite the Arozarena 2011 publication as providing the plausible biological mechanism for the association between PDE5 inhibitor use and melanoma. *Id.* at 226-228, 233-234.

Because Dr. Marais' opinions regarding his own publication are litigation-driven, they are not based on a reliable methodology and should be excluded.

### B. Dr. Marais's Opinions on the Biological Plausibility of Sildenafil or Tadalafil Use and Progression of Melanoma Are Based on an Incorrect Standard.

Dr. Marais's opinions countering Plaintiffs' experts' opinions on a biologically plausible mechanism of action are based on an incorrect standard—that a hypothesis must be proven in humans order to be biologically plausible. A plausible biological mechanism need not be shown with scientific certainty. *In re Hanford Nuclear Reservation Litig.*, 1998 WL 775340, at *7 (E.D. Wash. Aug. 21, 1998), ("'biological plausibility' is not the same as 'biological certainty . . . such certainty cannot be attained."), *rev'd on other grounds*, 292 F.3d 1124 (9th Cir. 2002). To require that a mechanism must be proven is incorrect. *See, e.g., Trasylol*, 2010 WL 1489730, at *7-8 (plausible biological mechanism need not be "proven" just "reliable," and using terms of "can" and "may" in regards to such does not render opinion unreliable); *Chantix*, 889 F. Supp. 2d at 1300 (mechanism theory deemed reliable despite "debate in the scientific community as to whether Dr. Bechara's dopamine depletion theory for Chantix can explain major depression and other neuropsychiatric injuries. . . . debate is not a basis for exclusion").

Dr. Marais applied an incorrect standard. In his view, "biological plausibility only arises when you have confirmation of the effect in people." JX 71, Marais Dep. at 85. For example, he testified as follows:

> Q. So I understand how you're using "biological plausibility," a proposed mechanism, in your view, is only biological plausibility when you have confirmation of cause and effect in a human patient? [Objection omitted]
>
> A: So I would only accept a biological plausibility when you have confirmation of response in patients if we're talking about drugs.

*Id*. at 88; *see also id.* at 83. In Dr. Marais' view, there can be no biological plausibility from only *in vitro* (cell) or *in vivo* (animal) experiments. In his report, he incorrectly stated: "[S]cientific evidence obtained from research strictly performed in the laboratory (based on cell and animal research) is not enough to draw reliable conclusions about whether the drug is associated with a particular outcome in humans." JX 27, Marias Rpt. at 20. It is Dr. Marais' opinion that biological plausibility can only arise when "you have confirmation of the effect in people." JX 71, Marais Dep. at 85.

His methodology is plainly wrong. *See, e.g., In re Heparin Prods. Liab. Litig.*, 2011 WL 2971918 (N.D. Ohio July 21, 2011) (animal data in conjunction with non-epidemiologic data can be sufficient to prove causation); *Ruff v. Ensigh-Bickford Indus., Inc.*, 168 F. Supp. 2d 1271, 1281 (D. Utah 2001) (affirming animal studies as sufficient basis for opinion on general causation); *see also* PX 37, *RMSE* at 664 and n.83 (*in vitro* cellular and tissue culture research "can be particularly helpful in identifying mechanisms of toxic action and potential target-organ toxicity" and *in vitro* research generally "can support opinions regarding whether the association between exposure and disease is biologically plausible"). Dr. Marais himself acknowledged that laboratory experiments are sufficient to establish a hypothesis. JX 71, Marais Dep. at 83, 87, 89. He admitted that cell experiments are useful to study transduction pathways relevant to a certain disease. *Id.* at 95. He agreed that cell experiments are useful to identify the molecular mechanisms that govern cell progression. *Id*. He agreed that laboratory tests with human or animal cells can be informative about isolated biological mechanisms. *Id*.

For the purpose of a causality assessment, these admissions are sufficient to establish biological plausibility. The criteria for a plausible biological mechanism set forth by Bradford-Hill requires scientists to examine whether there is a *plausible* biological mechanism, not a proven one. The literature is clear that a "hypothesis" may be sufficient to satisfy this criteria under Bradford-Hill. *See* PX 43, Douglas L. Weed & Stephen D. Hursting, *Biologic Plausibility in Causal Inference: Current Methods and Practice*, 147 AM. J. EPIDEMIOLOGY 415, 415-425 (1998). The *Reference Manual on Scientific Evidence* defines

"biological plausibility" as whether it is *plausible* that an agent causes a disease. PX 37, *RMSE* at 620. Likewise, the correct standard applicable to a determination of the overarching question of causality is "the preponderance of the evidence" and not "scientific certainty." *Allison*, 184 F.3d at 1312 ("the proponent of the testimony does not have the burden of proving that it is scientifically correct, but that by a preponderance of the evidence, it is reliable"); *Globetti v. Sandoz Pharms., Corp.*, 111 F. Supp. 2d 1174, 1180 (N.D. Ala. 2000) (application of the "scientific certainty" standard is "much too high a standard of admissibility" and "is far from what the Supreme Court intended in *Daubert*"); *Navelski v. Int'l Paper Co.*, 2017 U.S. Dist. LEXIS 44411, at *15-16 (N.D. Fla. Mar. 25, 2017) ("it would be unreasonable to conclude that the subject of scientific testimony must be 'known' to a certainty; arguably, there are no certainties in science.") (quoting *Daubert*, 509 U.S. at 590).

Dr. Maris turned the causality assessment on its head. He testified that "there's no evidence of causation which is what is required to provide biological plausibility." JX 71, Marais Dep. at 179. Although he insisted that confirmation in humans must come first in order to have biological plausibility, he acknowledged that confirmation in humans can be determined by observational studies. *Id.* at 85. Yet, in his cursory discussion of the many epidemiological studies establishing an association between PDE5 inhibitor use and progression of melanoma, Dr. Marais failed to make any assessment of the consistency of the association or the strength of the association in rendering his opinion on biological plausibility. *Id.* at 258. Moreover, his is a standard that in his mind will never be met—he has never read an epidemiological study that has concluded causation. *Id.* at 181.

Because he applied an incorrect standard to the biological mechanism factor, Dr. Marais' opinions regarding Plaintiffs' experts' causation analysis as to the biological mechanism should be excluded.

### C. Dr. Marais Lacks the Qualifications to Opine on Epidemiology and General Causation.

Dr. Marais has not stayed in his lane. His background as a molecular biologist does not qualify him to testify on general causation or to offer opinions on epidemiology. The Court should exclude his testimony on these topics.

"[T]he district court must decide whether the expert has 'sufficient specialized knowledge to assist the jurors in deciding the particular issues in the case.'" *Belk, Inc. v. Meyer Corp., U.S.*, 979 F.3d 146, 162 (4th Cir. 2012), *as amended* (May 9, 2012) (quoting *Kumho Tire*, 526 U.S. at 156). "Even the most qualified expert may not offer any opinion on any subject; the expert's opinion must be grounded in his or her personal 'knowledge, skill, experience, training or education.'" *Mullins*, 178 F. Supp. 3d at 900 (quoting FED. R. EVID. 702).

Dr. Marais readily admitted his lack of qualifications to opine on epidemiology. He agreed that he does not have any degrees in epidemiology. Dr. Marais also acknowledged that he is not an expert on epidemiology and that he deferred to defense experts that are epidemiologists for his assessments of the epidemiology:

> Q. Did you assess the consistency of the association reported in the observational studies?
>
> A. No, I did not. I defer to Dr. Witte and the experts in the field for those.
>
> Q. You defer to the epidemiological experts, correct?
>
> A. That is correct.
>
> Q. Of which you are not one, correct?
>
> A. Correct.

JX 71, Marias Dep. at 258.

It is no answer to say that Dr. Marais has read some articles on epidemiology. Of all of Dr. Marais many publications, he could only point to one publication that he had co-authored with an epidemiologist. *Id.* at 53. An expert's "review of literature in [an] area outside his field 'd[oes] not make him any more qualified to testify as an expert . . . than a lay person who read the same articles.'" *Siharath*, 131 F. Supp. 2d at 1351 (quoting *United States v. Paul*, 175 F.3d 906, 912 (11th Cir. 1999)). Nor can Dr. Marais point to any other training, skill, and experience that would provide the expertise to opine on general causation or epidemiology beyond biological plausibility. He is neither a clinician nor a toxicologist. JX 71, Marais Dep. at 51-52.

### D. Dr. Marais Did Not Apply a Reliable Methodology—or any Methodology at All—for His General Causation Opinions.

The trial court must "make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *See Kumho Tire*, 526 U.S. at 152. The trial court is required to do "a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue." *McClain*, 401 F.3d at 1237.

Dr. Marais offered only a cursory description of certain epidemiological publications and purported to offer the opinion "that the human data do not support the plaintiffs' assertion that sildenafil causes the progression of melanoma and the Plaintiffs' experts' opinions to the contrary are not reliable." JX 27, Marais Rpt. at 26-27. Dr. Marais' report contains no description of his methodology in reaching this causation opinion.

At his deposition, the reason for his failure to describe his methodology was clear—Dr. Marais admitted, repeatedly, that he did not conduct a causality assessment. He stated: "So, no, I did not undertake a causality assessment. As I mentioned, I am not an epidemiologist." JX 71, Marais Dep. at 219. He further testified: "So again, I deferred to the experts, particularly Dr. Witte, I read the manuscripts and I did not undertake my own causality assessment." *Id.* at 220.

The *Reference Manual on Scientific Evidence* makes clear that application of the Bradford-Hill factors is a proper method to assess general causation. *RMSE* at 597-600. Dr. Marais admitted he did not conduct any such Bradford-Hill analysis:

> Q: So you didn't conduct any sort of Bradford-Hill analysis, correct? [objection omitted]
>
> A. So no, I did not perform my own Bradford Hill assessment.

JX 71, Marais Dep. at 220.

Despite this clear and unequivocal testimony, on redirect, counsel for Pfizer attempted to have Dr. Marais testify that he did in fact undertake a causality assessment. But Dr. Marais failed to provide

any description of any methodology for this purported assessment, other than stating he conducted a "review of the literature" as set forth on pages 26-27 of his report. *Id.* at 255-258. Yet, Dr. Marais' report nowhere, much less than on these cited pages, describes in any way a methodology used for any sort of causal assessment. And, Dr. Marais again admitted that he did not perform a Bradford-Hill analysis. *Id.* at 255 ("I did not do a Bradford-Hill.")

Dr. Marais' "causation" opinions must therefore be excluded because he "has not identified any reliable method that he used to form these opinions." *Mullins,* 178 F. Supp. 3d at 901 (*citing Domingo ex rel. Domingo v. T.K.*, 289 F.3d 600, 607 (9th Cir. 2002)).

## IV. DR. LYNN SCHUCHTER (EXPERT FOR DEFENDANT PFIZER).

### A. Dr. Schuchter's Opinions Are Unreliable Because She Utilized No Clear Methodology and Substituted the Analysis of Others as Her Own.

Dr. Schuchter is a professor of hematology-oncology.[25] She offered opinions related primarily to Pfizer's clinical trials of sildenafil, the epidemiological literature, and specific attacks on Plaintiffs' experts based on her analysis of these two sources. This Court should exclude her testimony.[26] She provided no clear methodology by which she came to these opinions sufficient for this Court to assess their reliability. The closest Dr. Schuchter came to offering a glimpse into her methodology is where she stated that she had "evaluated the available scientific literature to determine whether there is reliable evidence of a causal relationship between Viagra use and melanoma progression." JX 30, Schuchter Rpt. at 15. Dr. Schuchter never detailed what evidence she considered, neither anywhere in her report nor subsequently in her deposition.[27]

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[25] *See Lynn Mara Schuchter, M.D.*, PERELMAN SCH. MED., https://www.med.upenn.edu/apps/faculty/index.php/g348/p15442 (last visited Jan. 10, 2019).

[26] At her deposition, Dr. Schuchter explicitly stated that she is not offering opinions on biological plausibility or the preclinical scientific literature and that she defers to other defense experts on those topics. *See* JX 69, Schuchter Dep. at 125-26, 237-41; s*ee* also JX 30, Schuchter Rpt. at 1-2 (not mentioning biologic plausibility or the preclinical scientific literature in her list of opinions offered). Accordingly, she should be precluded from offering any such opinions in this case.

[27] In fact, in her deposition Dr. Schuchter stated that she relied on her "review of the literature, the information that Pfizer counsel sent me, and the experts' reports." JX 69, Schuchter Dep. at 130. This statement fails to shed any light on what specifically she considered in forming her opinions aside from

Despite the requirement under Rule 26(a)(2)(B)(ii) that Dr. Schuchter disclose "the facts or data considered by the witness in forming [all opinions]," Pfizer instead disclosed a thirty-seven page list titled "Materials Received by Pfizer Inc.'s Experts" that was given to each of their experts, including Dr. Schuchter. JX 39. By its own title, this Court is left to assume that Pfizer's experts simply received, rather than read, the listed materials—something Dr. Schuchter confirmed to be the case in her deposition. JX 69, Schuchter Dep. at 28.[28] Far from clarifying the situation, this list only serves to further muddy the waters of what Dr. Schuchter actually considered.

As is problematic with other Pfizer experts, with respect to the epidemiological literature in particular, Dr. Schuchter's written report again merely re-hashed the analyses and conclusions of the studies themselves, offering little to no real opinion of her own. In doing so, she provided no framework for how she chose which studies to analyze or how she did, in fact, actually analyze each of the chosen studies. *See generally* JX 30, Schuchter Rpt. at 16-20. Nor does her report contain any commonplace methodology for analyzing epidemiological studies (such as, for instance, any mention of the Bradford-Hill criteria to assess causality). With no method for how Dr. Schuchter selected and set about analyzing each of the studies cited in her report, the Court cannot properly undertake its duty under *Daubert* to ensure that Dr. Schuchter's opinion comports with acceptable scientific principles in her field.

Further, one—if not the only—truly independent opinion Dr. Schuchter expressed regarding the epidemiological literature is wrong by her own admission. In her report, she opined that epidemiological studies are focused solely on "incident" melanoma, which according to her, cannot encompass melanoma "progression" as expressed by Plaintiffs' experts. To the contrary, Dr. Schuchter testified that the term "progression" can include a melanoma lesion transitioning from undetectable to detectable and, as such, it would be incorporated in the term "incident" as used in the epidemiological literature. *See* JX 69,

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unspecified materials fed to her by Pfizer's attorneys. As discussed *infra* p. 44 such a heavy reliance on Pfizer generated documents is a hallmark of unreliability itself.

[28] When being questioned about the materials list provided by Pfizer versus what she actually considered, Dr. Schuchter stated, "I listed in my report, I think, the most important papers." JX 69, Schuchter Dep. at 28.

Schuchter Dep. at 207-211.[29] Whether Dr. Schuchter merely made a mistake or was intentionally deceptive in her report is beside the point for purposes of this motion. It is not possible based on the evidence provided by Pfizer for this Court to properly assess the reliability of Dr. Schuchter's opinions and they must be excluded.

Additionally, Dr. Schuchter's opinions related to Pfizer's sildenafil clinical trials should be excluded because Dr. Schuchter did nothing more than review Pfizer-generated summary documents and parrot their results in her report. Dr. Schuchter may have experience in conducting clinical trials and evaluating their results, yet, despite any such experience, the section in her report discussing the clinical trials contains just two short paragraphs which both cite a Pfizer-generated summary document provided to her by Pfizer's counsel. JX 69, Schuchter Dep. at 21, 44-46, 89-94. Simply accepting as fact summary data provided to her by Pfizer's attorneys is not what an experienced scientist like Dr. Schuchter would do outside of a litigation context. Such blind reliance clearly sets her opinions on Pfizer's clinical trials in the province of impermissible, litigation driven opinions of the type *Daubert* and its progeny are

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[29] Dr. Schuchter admitted that most melanomas originate with one mutated cell or small group of cells, and that there are limits to the detectability of such early melanomas: "Well, again, because so often it's arising in a precursor mole—so remember a precursor mole already—a nevus already has a lot of genetic abnormalities. And so while it does tend to be clonal, meaning that it starts from a series of cells from that particular nevus, I guess at some point there could be—there is obviously one cell before it divides until there's multiple cell -- hard to find one cell."

Dr. Schuchter went on to say that such cell division in early melanomas is progression of the disease:

> Q: Yeah. I'm just trying to make sure we have our terms straight. So we were talking about this one cell that starts dividing and then creates this larger population of cancer cells. That's progression of the disease, right?
>
> A: That's correct."

JX 69, Schuchter Dep. at 210-211.

Dr. Schuchter also conceded that such progression would have been captured in the epidemiological literature she discussed—a direct contradiction with her report:

> Q: I'm just trying to make sure—I'm trying to connect the two things we've been talking about here for the last ten minutes or so. When you say—when you say these people have new melanoma or incident melanoma, that would be a melanoma that has progressed to the point where it's clinically detectable or diagnosable, right?
>
> A: Correct.

*Id.* at 221

specifically intended to exclude. This unreliability notwithstanding, Dr. Schuchter conceded in her deposition that none of the clinical trials she referenced in her report were designed in a way that would allow them to detect melanoma. *Id*. at 97-98.[30] Not only is her opinion litigation-driven, but it is also irrelevant with respect to melanoma. Both reasons warrant exclusion.

Finally, Dr. Schuchter's attacks on Plaintiffs' experts should also be excluded because they are clearly based on the impermissible opinions described above. Dr. Schuchter offers six specific critiques of Plaintiffs' experts, yet all but one of these criticisms are related to her flawed opinions on the clinical trial data or epidemiological literature. The only criticism she offers on a different topic is that Plaintiffs' experts "improperly interpret" evidence related to the alleged anti-cancer effects of PDE5 inhibitors. JX 30, Schuchter Rpt. at 32. As discussed *supra* p. 40-45, these studies are irrelevant to the question at hand. Thus, there is no sound basis for allowing any of her criticisms of Plaintiffs' experts.

The above issues with Dr. Schuchter's proposed testimony make more sense when viewed in the context of her extensive ties to the pharmaceutical industry. Dr. Schuchter admitted in her deposition that she has testified multiple times for pharmaceutical companies and that she has performed consulting work for pharmaceutical companies for decades. JX 69, Schuchter Dep. at 1-17, 73-74. This type of bias supports the argument that Dr. Schuchter's opinions do not pass muster. For all these reasons, the entire bases for Dr. Schuchter's opinions are unreliable, and this Court should accordingly preclude Dr. Schuchter from offering any opinions in this litigation.

## V. DR. MARIA WEI (EXPERT FOR DEFENDANT PFIZER).

### A. Dr. Wei Is Not Qualified to Opine on Epidemiology and General Causation.

Dr. Wei's opinions on causality and any reference to the lack of a causal relationship between PDE5 inhibitors and melanoma should be excluded. She is not qualified to provide an opinion on epidemiology or general causation.

"[T]he district court must decide whether the expert has 'sufficient specialized knowledge to assist the jurors in deciding the particular issues in the case.'" *Belk*, 979 F.3d at 162, *as amended* (May 9, 2012)

[30] Schuchter admitted the clinical trials "were not designed to detect melanoma. They were designed to test, you know, efficacy for erectile dysfunction or other conditions." JX 69, Schuchter Dep. at 97-98.

(quoting *Kumho Tire*, 526 U.S. at 156). "Even the most qualified expert may not offer any opinion on any subject; the expert's opinion must be grounded in his or her personal 'knowledge, skill, experience, training or education.'" *Mullins*, 178 F. Supp. 3d at 900 (quoting FED. R. EVID. 702).

Here, Dr. Wei lacks the basic qualifications to provide a causation opinion. Dr. Wei's training in epidemiology is *limited to a single semester course*. JX 75, Wei Dep. at 161:19-163:7. Nonetheless, Dr. Wei astoundingly claimed to be an epidemiologist as it relates to the skin:

> Q. [D]o you consider yourself to be an expert in epidemiology?
>
> A. It's a rather limited question in the sense that I do research in epidemiology. I publish in epidemiology. So in a limited sense, I am an epidemiologist of the—of skin disorders. You know, it's so broad. So I don't consider myself an expert in other areas of epidemiology. But for the skin, yes, I do epi studies in the skin.

*Id.* at 104:23-105:2. Even if one considers the totality of Dr. Wei's experience including her one semester course in epidemiology, epidemiology research, and limited epidemiology publications in which she is listed, Dr. Wei hardly rises to the level of an expert in epidemiology.

**B. Dr. Wei Failed to Apply a Reliable Methodology to Opine on Causality**

Although Dr. Wei purports to give an expert opinion on general causation, her opinion is not based on any sort of causal assessment using a reliable methodology. Dr. Wei's report fails to identify the methodology she purported to use in reaching her causality conclusions. *See generally* JX 33, Wei Rpt. Dr. Wei failed to analyze or even discuss Bradford-Hill criteria. *See id.* Instead, she merely summarized data, then criticized the laboratory studies and Plaintiffs' experts. Instead of supporting her opinion on causality with a detailed analysis and explanation that would allow this Court to identify the methodology used and assess the reliability thereof, Dr. Wei's report merely summarized scientific data and made conclusory statements. *See generally* JX 33, Wei Rpt. These flaws render her opinions on causality unreliable and worthy of exclusion.

The trial court must "make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *See Kumho Tire*, 526 U.S. at 152. It is well-

settled law that for an expert's opinion on causality to be accepted, the expert must have performed a causal assessment to explain how they ultimately reached their opinions. The Ninth Circuit has affirmed the exclusion of expert opinions on causality where the expert only conducted an "extremely thin" analysis of Bradford Hill's criteria. *See Orrell*, 662 Fed. App'x 528.

As is the case with most of Pfizer's other experts, the section of Dr. Wei's report addressing the scientific literature dealing with PDE5 inhibitors and melanoma is little more than a recapitulation of the data from each study and a copy and paste of the authors' conclusions. *See generally* JX 33, Wei Rpt. In doing so, Dr. Wei provided no appreciable analysis of her own, no causality assessment, and no methodology by which she reached her ultimate conclusion that no causal relationship exists between PDE5 inhibitors and melanoma progression. For example, in summarizing her findings based on the observational studies, Dr. Wei provided several criticisms of the Li 2014 study that found the strongest association between PDE5 inhibitor use and melanoma, yet she mentioned nothing about weaknesses in her discussion of the four other studies mentioned in her report (Loeb 2015, Matthews 2016, Pottegård 2016, Lian 2016). JX 33, Wei Rpt. at 15. She notes that these other four studies are "much larger population-based studies" and then inexplicably concludes that "the totality of the observational studies does not support a conclusion that sildenafil causes melanoma initiation or progression." *Id.* This type of review provides no analysis and no insight as to how she weighted each study or used such weighting to consider and arrive at a causality opinion.

Dr. Wei's mere recitation of clinical and observational data and her failure to provide any causality assessment, such as a discussion of Bradford-Hill criteria, makes it impossible to determine her methodology and the reliability thereof. Further, Dr. Wei lacks the qualifications to offer an opinion on causality. Her opinions on causality do not meet even the minimum standards of this Court. Dr. Wei's opinions on, or any inferences to, a causal relationship between PDE5 inhibitors and melanoma should be excluded.

## VI. DR. KARLA BALLMAN (EXPERT FOR DEFENDANT ELI LILLY).

### A. Dr. Ballman is Not Qualified to Give an Epidemiology Opinion.

Dr. Ballman is not an epidemiologist, has not taken any courses in epidemiology, has never taught courses in epidemiology, and does not have even a working understanding of basic epidemiology concepts—a fact confirmed by *Pfizer's* epidemiologist. Shockingly, in order to mislead this Court, Dr. Ballman blatantly misrepresents both her educational experience and her qualifications in her report and *curriculum vitae*, undermining not only her reliability as an expert, but also her basic credibility as a witness.

Upon a superficial review of her expert report, Dr. Ballman appears qualified to offer an opinion on the epidemiology showing an increased risk between PDE5 inhibitors and the development of melanoma. Her "qualifications," however, are mere pretense. Dr. Ballman knowingly misrepresented her fitness as an expert in an attempt to offer opinions outside her area of expertise. Moreover, she lacks the requisite experience, training, education, and credibility necessary to provide reliable testimony to the trier of fact. Dr. Ballman is unfit to serve as an expert and should be disqualified.

#### 1. Dr. Ballman Mischaracterized Her Education and Experience in Epidemiology.

In attempting to qualify as an epidemiology expert in this litigation, Dr. Ballman fundamentally embellished her credentials. As described in her report, she is a tenured professor of biostatistics and currently serves as Division Chief of Biostatistics and Epidemiology at Weill Cornell Medicine. JX 41, Ballman Rpt. at 2; JX 81, Ballman Dep. at 19:2-12, 26:19-23. She does not, however, have a degree in epidemiology. *See* JX 41, Ballman Rpt. at 2; JX 81, Ballman Dep. at 35:19 to 36:8. She claimed, instead, to have completed "substantial training in statistics and epidemiology" while obtaining her degree in Operations Research from the Massachusetts Institute of Technology ("MIT"). JX 41, Ballman Rpt. at 2. Yet, when questioned about the "substantial training" she supposedly underwent, ***Dr. Ballman could hardly remember taking one course, if she did at all***:

> I don't remember what the name of the course was in particular. There was a course taught basically in terms of identifying and understanding biases in studies. ***It might have been a seminar or something.***

JX 81, Ballman Dep. at 38:7 to 39:7. Further, a review of MIT's Course Requirements in the field of Operations Research reveals that no epidemiology courses were required to obtain her degree, and in fact, epidemiology is not even offered as a major at MIT. *Id.* at 35:19-22, 38:15 to 39:17.

Dr. Ballman also lied about her experience teaching epidemiology. In her report, she claimed to have "taught several statistics and epidemiology courses" while serving as a faculty member at the University of Auckland in New Zealand.[31] JX 41, Ballman Rpt. at 2. However, Dr. Ballman's former colleague and course coordinator for the University, David Smith, could not remember a single epidemiology lecture she ever taught. *See* JX 81, Ballman Dep. at 40:24 to 41:5, 41:9-18. Tellingly, Dr. Ballman herself could not remember whether she taught an actual course in epidemiology or just gave a lecture. *Id.* at 40:2-18 ("I'm not sure I can remember all the name[s] of the courses I taught. . . . I don't remember the name of it and, at this point, I don't know if it was a formal degree-bearing course or whether it was just sort of a seminar."). She ultimately admitted in her deposition that she never specifically taught ***any*** let alone "several" epidemiology courses; rather, she only taught statistics courses that "touched upon epidemiological concepts." *Id.* at 42:19-23, 43:1-10.

Further, Dr. Ballman deceptively edited her resume to make herself appear more qualified. Specifically, she added fictional epidemiology references to her *curriculum vitae*. For example, when Dr. Ballman appeared as an expert in a 2017 patent litigation, her submitted report did not include any information regarding her supposed experience teaching epidemiology courses. *Id.* at 40:2-7. By contrast, her recent *curriculum vitae* and expert report allege that she has had a robust career in epidemiology, having taught several statistics ***and epidemiology courses***. *See id.* at 39:18-23; JX 41, Ballman Rpt. at 2 (emphasis added).

Dr. Ballman's testimony reveals a lack of relevant education, training and experience required to offer a reliable opinion—not to mention the fact that it showcases her willingness to flagrantly misrepresent the truth about her lack of experience to this Court. As such, she is both discredited and unqualified to opine on epidemiological principles and therefore her testimony should be excluded.

[31] Her official title was Lecturer in Statistics. JX 81, Ballman Dep. 40:19-22.

**2. Dr. Ballman Distorted Her Knowledge and Understanding of Melanoma to Bolster Her (Lack of) Qualifications.**

In her report, Dr. Ballman claimed to have worked in several areas of cancer research, including melanoma. JX 41, Ballman Rpt. at 3; *see also* JX 81, Ballman Dep. at 45:6-23. She further purported to be an active collaborator on studies involving "clinical trials, cancer biomarkers, and observational studies for cancer risk factors." JX 41, Ballman Rpt. at 2. Yet, the single article she published on melanoma[32] focused not on the disease itself, but on determining why physicians failed to comply with treatment guidelines. JX 81, Ballman Dep. at 46:8-47:6, 49:24-50:22. The article was wholly unrelated to risk factors for developing melanoma, a key component in this litigation. *Id.* at 51:9-14.

The overall majority of Dr. Ballman's work focuses on different kinds of cancers not at issue in this litigation.[33] *Id.* at 46:2-7. She is unfamiliar with the causal mechanism of melanoma, but instead of being forthcoming, Dr. Ballman misrepresented her expertise in an attempt to fraudulently bolster her qualifications. For this additional reason, she should be excluded from testifying in this litigation.

**B. Dr. Ballman Did Not Employ a Reliable Methodology to Reach Her Conclusions.**

Dr. Ballman fails to satisfy the threshold of having utilized an accepted methodology. Her purported "application" of the Bradford-Hill methodology has a number of fatal flaws. *Mirena,* 2018 U.S. Dist. LEXIS 182420, at *184. Dr. Ballman provides a cursory analysis of epidemiological studies purporting to use the Bradford-Hill method, but she is ignorant to its proper application.

To start, Dr. Ballman misconstrues step one of the Bradford-Hill method. "[E]pidemiologists use a two-step process for establishing general causation." *In re Lipitor (Atorvastatin Calcium) Mktg. Sales Practices and Prods. Liab. Litig.*, 145 F. Supp. 3d 573, 576 n.2 (D.S.C. 2015); *see also Ambrosini v. Labarrque*, 101 F.3d 129, 136 (D.C. Cir. 1996). First, observational studies must demonstrate an

[32] Although she had only published one article on melanoma, Dr. Ballman claimed she had worked on "some clinical trial designs in melanoma" during her time at the Mayo Clinic. JX 81, Ballman Dep. at 47:8-19. She admitted, however, that her work was never published since it was assigned to another individual once she left her position at the Clinic. *See id.* What little work she may have performed on the trials was never completed.

[33] In general, Dr. Ballman's work focused on breast cancer, prostate cancer, lung cancer and sarcoma. *Id*. at 46:2-7.

association between two variables. *See In re: Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prods. Liab. Litig. (No. II) MDL 2502*, 892 F.3d 624, 640 (4th Cir. 2018); *Dunn v. Sandoz Pharms. Corp.*, 275 F. Supp. 2d 672, 679 (M.D.N.C. 2003) ("If two variables correlate, the incidence of one variable changes with the incidence of another. In other words, one variable increases the risk of the other."). Once a positive association is established, epidemiologists apply a set of factors, commonly referred to as the "Bradford-Hill criteria," to evaluate whether the observed association between the variables is causal. *See Fosamax*, 645 F. Supp. 2d at 187; *Mirena*, 2018 U.S. Dist. LEXIS 182420, at *182; *In re Lipitor*, 892 F.3d at 640.

Instead, Dr. Ballman employed *her* incorrect understanding of the basic principles of epidemiology. Turning a blind eye to the observational studies' findings, Dr. Ballman claimed the studies do not establish a "clear-cut" association and therefore found they do not meet her made-up "preliminary" threshold to even apply the Bradford-Hill criteria. *See* JX 41, Ballman Rpt. at 42. Dr. Ballman's denial of association is objectively wrong and relies on her disregard of the consistent body of positive epidemiology that has repeatedly observed a correlation between the use of PDE5 inhibitors and an increased risk of melanoma.

Dr. Ballman's application of Bradford-Hill's first prong was misguided and demonstrates her lack of understanding of proper methodology. In determining whether an association exists, Dr. Ballman employed another fabricated method she describes as a "sniff" test. JX 81, Ballman Dep. at 205:6-18 ("I'm saying that a clear-cut association may—may involve looking at strength, but it also involves sort of doing what people like to call a sniff test, whether or not what you're seeing makes reasonable sense and whether there could be some confounding that could explain the association."). Her use of a so-called "sniff" test is unsupported and not methodologically sound. Dr. Ballman justified substituting her "sniff" test for established Bradford-Hill criteria with "[her] experience"—itself already discredited. *Id.* at 198:16-22. Needless to say, the "sniff" test is not an accepted methodology, especially coming from an individual lacking expertise in melanoma and epidemiology. *See Daubert*, 509 U.S. at 593-94; *Carnegie Mellon Univ. v. Hoffman-LaRoche, Inc.*, 55 F. Supp. 2d 1024, 1029-30 (N.D. Cal. 1999) (identifying one of the

factors for assessing the scientific validity of an expert's testimony as "whether the theory or technique is generally accepted within a relevant scientific community").

Rather than Dr. Ballman's "sniff" test, Bradford-Hill requires that an association be "beyond what we would care to attribute to the play of chance." JX 102, Hill 1965 at 295. The method scientists use to examine the role of chance is that of statistical significance. A statistically significant result means that, with 95 percent certainty, the observed result or association is not due to chance. *See Magistrini* 180 F. Supp. 2d at 592. Here, there are multiple studies with statistically significant results showing the association between PDE5 use and melanoma development. The role of chance as an explanation for the repeated observed associations across different populations is accounted for and virtually impossible.

Third, Dr. Ballman improperly employed the role of confounding as part of her "sniff" test. It is clear from both her report and her deposition that Dr. Ballman does not have a clear understanding of what confounding means. She found, for example, even an elementary explanation of the concept "quite dense." Regardless, Dr. Ballman, in an effort to explain away the statistically significant results observed in different populations, different time frames and using different methods, summarily blames confounding.[34]

Fourth, Dr. Ballman admitted that she cherry-picked, acknowledging that she did not conduct a full Bradford-Hill causation analysis:

> Q: [Y]ou're saying, if something doesn't meet the sniff test, you don't apply the nine Bradford-Hill criteria, correct?
>
> A: But I'm saying, part of the sniff test might overlap with some of the criteria within the Bradford-Hill.
>
> Q: So you are actually applying some of the criteria, but not all of them, is that right?
>
> A: I'm saying, if you don't pass the major ones, there's no need to go on and apply the other ones.

[34] The concept of confounding is that there is another, unrelated variable that can explain the observed association. *See* PX 42, MOD. EPIDEMIOLOGY 2008 at 132-34.

JX 81, Ballman Dep. at 209:4-16. In her report itself, Dr. Ballman confessed that she only "briefly" reviewed the factors she herself deemed "most relevant to [an] epidemiological analysis." JX 41, Ballman Rpt. at 42-45 (considering only five of the criteria without explaining any reason for omitting the others).[35] Not only is her methodology of selectively applying the Bradford-Hill criteria inappropriate, it is not supported anywhere in the literature or in Bradford-Hill's pivotal publication. While each criteria need not be satisfied in order to reach a reliable causation opinion, cherry-picking a few is not proper methodology.[36] *See Orrell*, 662 Fed. App'x at 530; *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 466, 480-81 (E.D. Pa. 2014) (holding that since "the experts did not adequately consider the Bradford-Hill criteria as a whole, [their] causal conclusions were not formed using a reliable scientific method."). Since Dr. Ballman chose not to adequately consider the Bradford-Hill criteria as a whole, her causal conclusions were not formed using a reliably scientific methodology. *See In re Zoloft*, 26 F. Supp. 3d at 480-81.

Finally, Dr. Ballman's plainly incorrect assessment of the epidemiological results further exposes her result-driven approach. In her report, Dr. Ballman wrongly stated that "[o]bserved associations for PDE5 exposure and risk of melanoma are not consistent across the studies, except in being weak or non-existent." JX 41, Ballman Rpt. at 38. To the contrary, each observational study reported associations, many statistically significant, between PDE5-inhibitor use and an increase in melanoma. Further, every meta-analysis conducted observed a statistically significant association between the two variables. Rather than account for statistically significant associations, Dr. Ballman simply rejects them outright due to supposed "chance, bias or confounding." JX 41, Ballman Rpt. at 42. These criticisms are baseless. First, while each observational study differed on the types of controls utilized, they all controlled for

[35] Arguably, Dr. Ballman mentions a sixth criteria (biological plausibility) in a separate section of her report. *See* JX 41, Ballman Rpt. at 39-40. However, her opinion was not analyzed according to the Bradford-Hill methodology.

[36] *See also* JX 102, Hill 1965 at 299:

> None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?

confounding. *But see Abilify*, 299 F. Supp. 3d at 1322 ("Failure to control for every conceivable potential confounder does not necessarily render the results of an epidemiological study unreliable."). Second, Dr. Ballman herself later conceded that a statistically significant finding would unlikely be due to random error or chance. JX 81, Ballman Dep. at 191:21 to 195:3.

"Result-driven analysis, or cherry-picking, undermines principles of the scientific method and is a quintessential example of applying methodologies (valid or otherwise) in an unreliable fashion." *In re: Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prods. Liab. Litig. (No. II) MDL 2502*, 892 F.3d 624, 634 (4th Cir. 2018); *see Accutane*, 191 A.3d at 592. Despite the number of studies establishing an association between PDE5 inhibitors and melanoma, Dr. Ballman summarily dismissed their findings as "unusual." JX 81, Ballman Dep. at 211:2-9, 212:6-13 ("I'm saying, for myself, in my studies, if I have an association for which it's unusual, it's the first time we've seen it, and there is the evidence of residual confounding, that it wouldn't make sense for me to apply other criteria to go on and say that there is a causal relationship."). Here again, Dr. Ballman directly contradicted Bradford-Hill's guidelines by conflating association with causation.[37] In her report, she argued that "a statistically significant point estimate above 2, and preferably 3, across several studies is required before most investigators believe there may be a causative effect." JX 41, Ballman Rpt. at 8.[38] Further, she opined that point estimates less than 2.0 are evidence of a weak association.[39] *See id.* Not only does she fail to provide adequate support for her assumptions, controlling case law directly contradicts her proposition; "[w]here the study properly accounts for potential confounding factors and concludes that exposure to the agent is what increases the probability of contracting the disease, the study has demonstrated general causation—that exposure to the agent is capable of causing [the illness at issue] in the general population." *Bextra & Celebrex*, 524 F. Supp. 2d at 1172-73 (further explaining that a relative risk of greater than 1.0 is probative of general

[37] *See* JX 102, Hill 1965 at 296 (cautioning epidemiologists to avoid eagerly dismissing causal hypotheses even if an observed association appears slight).

[38] Dr. Ballman could not provide a citation to support her argument. *See* JX 81, Ballman Dep. at 215:21 - 217:2 ("Sorry. I misspoke. I didn't mean I could give you a reference that most investigators believe this. I could give references where people say generally if the – if the point estimate is not that high, that there – it will not be a cause – causal factor.").

[39] *But see* PX 35, Craun, G.F. & R.L. Calderon, *How To Interpret Epidemiological Associations*, (2006) (noting that point estimates over 1.5 are considered "Moderate to Strong" associations).

causation, while a relative risk of 2.0 can be probative of specific causation); *Roundup*, 2018 U.S. Dist. LEXIS 114760, at *128 n.30. Since each observational study and meta-analysis consistently observed point estimates greater than 1.0, an association has been established between PDE5-inhibitor use and melanoma.

### C. Dr. Ballman's Lack of Basic Knowledge of Epidemiologic Principles Make Her Opinions on Confounding Unreliable.

Testimony from an expert who herself does not understand basic, fundamental principles within the relevant field of science, will only serve to mislead the jury. Dr. Ballman repeatedly stated throughout her report that confounding factors are an explanation for the associations demonstrated between PDE5 inhibitor use and melanoma progression. Yet, Dr. Ballman's opinions on confounding variables as they apply to risk factors displayed a level of confusion and unreliability warranting exclusion.

According to the widely-accepted authority in the field of epidemiology, a variable must satisfy three necessary characteristics to be deemed a confounding factor:

1. A confounder must be an extraneous risk factor for the disease;
2. A confounding factor must be associated with the exposure under study in the source population (the population at risk from which the cases are derived); and
3. A confounding factor must not be affected by the exposure or the disease.

PX 42, MOD. EPIDEMIOLOGY 2008 at 132. Most importantly, as expressed in the third criteria, a confounder cannot be an intermediate, or mediating, factor of the disease.

In her report, Dr. Ballman asserted that people of higher socioeconomic status have a greater risk of developing melanoma. *See* JX 41, Ballman Rpt. at 4 ("A . . . logical and biologically plausible explanation is that people with higher incomes are also more likely to have intermittent sunburns, a known risk factor of melanoma, due to leisure activities and vacation exposure."). From this, she concluded that the number of sunburns would necessarily be a confounding variable. *See id.*; JX 81, Ballman Dep. at 179:2-6. This opinion, however, directly contradicts a basic premise in epidemiology—a confounder cannot be an intermediate step in the causal pathway between the exposure and the disease.[40] The only

[40] *See* PX 42, MOD. EPIDEMIOLOGY 2008, *supra* note 19.

way, in this example, that socioeconomic status could lead to higher melanoma rates is *through* sun exposure, meaning that sun exposure is in the pathway between socioeconomic status and melanoma development. Dr. Ballman's understanding of this very basic epidemiology principle of confounding is patently incorrect.

Further demonstrating her lack of knowledge of basic epidemiological principles, Dr. Ballman did not understand the difference between a confounding factor and mediating factor. While Dr. Ballman's report depicted a diagram to convey her opinions related to the concept of confounding, the diagram showed a *mediating factor* rather than a *confounding factor*. JX 41, Ballman Rpt. at 5. When asked whether Dr. Ballman intended to illustrate a mediating factor rather than a confounding factor, she insisted her understanding was correct and that it showed confounding. *Id* at 4; JX 81, Ballman Dep. at 177:10 to 183:24. Dr. Ballman's testimony and understanding of confounding, however, was completely refuted by Dr. John Witte, PhD, an epidemiologist retained by Pfizer. According to Dr. Witte, a confounding variable should not be in the mediation pathway.[41] JX 73, Witte Dep. at 59:20-23. Further, when presented with the diagram in Dr. Ballman's report, which she had insisted illustrated confounding, Dr. Witte disagreed with her (and agreed with Plaintiffs), confirming it showed a mediating factor. *Id.* at 86:11-19. Dr. Ballman cannot possibly assist a trier of fact when she herself lacks the proper understanding of basic epidemiological principles.

### D. Dr. Ballman's Opinions on Biological Plausibility Should Be Excluded as Unreliable and Unsupported.

Biological plausibility is a credible scientific explanation for the process by which a drug has the potential to cause a particular disease in the human population. *See Abilify*, 299 F.Supp.3d at 1308. The potential mechanism of action, however, need not be definitively proven. *See id.* (quoting *Daubert*, 509 U.S. at 590 ("Of course, it would be unreasonable to conclude that the subject of scientific testimony must

[41] It is important to note, however, that a confounder may sometimes be found in the causal pathway between the exposure and disease ("confounding by intermediate variables"). *See* JX 73, Witte Dep. at 59:14-19. This type of confounding may apply in situations with time-dependent factors. However, as Dr. Witte correctly recognized, that situation does not exist in the epidemiological studies subject to this litigation. *Id.* at 60:2-3.

be 'known' to a certainty; arguably, there are no certainties in science.")); *see also Jones v. Otis Elevator Co.*, 861 F.2d 655, 662 (11th Cir. 1988) (holding that "absolute certainty is not required" from an expert's testimony). Per Bradford-Hill: "It would be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand."[42]

Dr. Ballman's argument against a plausible mechanism of action failed to adequately consider all relevant material on the subject. Dr. Ballman offered a superficial review of the biological mechanism of PDE5 inhibitors, rejecting that they could impact melanoma development simply because they do not cause *other non-melanoma* diseases. JX 41, Ballman Rpt. at 39-40; JX 81, Ballman Dep. at 231:1-7, 264:16-24, 265:1-2 ("[I]f there is biological plausibility or a cause-and-effect mechanism, one would expect it to be seen in other diseases that are treated with PDE5i inhibition and it's not seen there.").[43]

In reaching her conclusion, Dr. Ballman only considered two mechanism studies. JX 81, Ballman Dep. at 233:1-20. She did not consider any further preclinical scientific evidence, and failed to even mention Dhayade 2016 in her report. *Id.* at 295:7 to 297:3; JX 41, Ballman Rpt. at 39-40. Dhayade 2016 tested and identified potential pathways that linked PDE5 inhibitor use to melanoma progression. Though she claimed to have considered the study, Dr. Ballman could not provide an adequate explanation as to why she chose to disregard its findings. JX 81, Ballman Dep. at 241:11-18 ("I wasn't convinced. . . . [and] didn't think the evidence was compelling that they could definitely conclude [that sildenafil promotes melanoma growth]."). That she "wasn't convinced" by the study is conclusory and not a proper analysis.

Further, as noted above, the biologic plausibility of PDE5 inhibition and melanoma development has been hypothesized, demonstrated, and accepted in several published, peer-reviewed studies (as well as in statements of the FDA, Pfizer, and Eli Lilly). Dr. Ballman dismissed statements accepting the plausible mechanism of action in epidemiological studies as nothing more than hypotheses "used in

[42] JX 102, Hill 1965 at 298.

[43] Bradford-Hill cautions that observed associations may be novel and must not be dismissed "too light-heartedly." JX 102, Hill 1965 at 296. *See also Wendell v. GlaxoSmithKline LLC*, 858 F.3d 1227, 1237 (9th Cir. 2017) ("Not knowing the mechanism whereby a particular agent causes a particular effect is not always fatal to a plaintiff's claim."); *Kennedy v. Collagen Corp.*, 161 F.3d 1226, 1229-30 (9th Cir. 1998) ("Thus, even if the medical evidence asserts 'only' an association . . . plaintiffs' experts' testimony should not be excluded if they adequately explain why the association is valid and how causation can be inferred from it.").

background to motivate why they're doing the particular study." JX 81, Ballman Dep. at 244:20-21, 247:6-15. Of course, the fact that there is a plausible mechanism of action (as shown in Arozarena 2011 and other studies) *is the very reason why scientists created epidemiology studies to investigate potential associations between sildenafil and tadalafil use and melanoma incidence.* Dr. Ballman conceded as much in her deposition, contradicting her claimed lack of plausibility. *Id.* at 243:10-12 ("[G]iven that they have written this in the manuscript, I guess I am led to believe that they do believe [a causal connection] is possible.").

When confronted with the FDA's conclusion that "[w]e acknowledge ***there may be a biologically plausible mechanism*** for PDE5 inhibitors and melanoma," PX 19, FDA00000001 at 11 (emphasis added). Dr. Ballman hesitated slightly before she disagreed with the FDA. JX 81, Ballman Dep. at 235:14-20, 235:20-24, 236:1-15. She could not, however, offer any explanation as to why her opinion differed from the FDA's findings:

> Well, again, I'm not sure, just off the top of my head, of all the information that they looked at, but I—in my definition of biological plausibility and **whether we're seeing sort of a cause and effect in humans, I do not believe there is a biological[ly] plausible mechanism for this**.

*Id.* at 235:18 to 236:1 (emphasis added). The most detrimental part of her failed explanation is it shows she does not understand the concept of biologic plausibility—her stated definition of biologic plausibility incorrectly requires "a cause and effect in humans."

### E. Dr. Ballman Made a Number of Substantial Errors Rendering Her Report Unreliable.

Whether basing their opinions on professional studies or personal experiences, experts must "employ . . . in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire*, 526 U.S. at 152. Despite claiming that she applied the same rigorous techniques and level of precision used in her normal course of work, Dr. Ballman presented to this Court a report that undoubtedly falls below the standard required under *Daubert*. Ballman Dep. at 165:14-17, 166:17-23. Dr. Ballman's report is rife with unsubstantiated errors coupled with inaccurate and inconsistent testimony, rendering her opinions patently unreliable.

In her most egregious error, Dr. Ballman offers several "factual" assertions that are either (1) improperly cited and therefore, unsupported; or (2) blatantly mischaracterized. For example, as support for her claim that the prevalence of melanoma in the United States varies by race, Dr. Ballman cites to a SEER Cancer statistics report on "myeloma." JX 41, Ballman Rpt. at 12, 49. Though similar in appearance to "melanoma," *myeloma is an entirely different type of cancer* (it affects plasma cells and prevents the normal production of antibodies, thereby weakening the human immune system).[44]

In her second most egregious error, Dr. Ballman erroneously cites to an article in an attempt to discredit Plaintiffs' epidemiology expert Dr. Feng Liu-Smith. JX 41, Ballman Rpt. at 26. In contrast to Dr. Liu-Smith's claims that solar keratosis is not a valid negative control, Dr. Ballman offers a citation purporting to find solar keratosis "independently indicative of melanoma, with an odds ratio of 4.7 (95% CI: 2.0 – 10.9)." *See id.* However, the point estimate reported in the article was associated with "the presence of 10 or more solar keratosis on the left forearm (compared with none)."[45] Dr. Ballman's statement badly misrepresents the findings in the study—the four-fold increase in risk applied to a localized region of the human body, and should not have been used to infer an overall indication.

While Dr. Ballman explained that her reviewers would normally edit out typographical mistakes. JX 81, Ballman Dep. at 165:18-22, her inaccuracies are far more serious than mere "typos." *See id.* at 166:24 to 167:3. "The proponent of an expert is required to show that the witness's testimony is based on something 'more than subjective belief or unsupported speculation.'" *Townsend v. Monster Bev. Corp.*, 303 F. Supp. 3d 1010, 1032 (C.D. Cal. 2018) (quoting *Daubert*, 509 U.S. at 590 (1993)). Frequently throughout her testimony, she admitted that her contentions could not be supported based on the citations she provided. JX 81, Ballman Dep. at 133:22 to 134:4, 156:14 to 157:14, 158:13-20. Having asserted she spent over one-hundred forty hours preparing her report, seventy hours of which were spent writing, Dr.

[44] *Myeloma*, AM. SOC'Y HEMATOLOGY, http://www.hematology.org/Patients/Cancers/Myeloma.aspx (last visited Jan. 10, 2019).

When confronted with her error during her deposition, Dr. Ballman dismissed it as merely an oversight. Ballman Dep. at 133:7-12. However, Plaintiffs' counsel reviewed both the myeloma and melanoma statistics reported by SEER and could not discern where she obtained her information. Since the statistics in her report could not be independently verified, her contentions remain unsubstantiated.

[45] PX 36, Bataille *et al.*, *Solar Keratosis: A Risk For Melanoma But Negative Association With Melanocytic Naevi*, INT'L J. CANCER 8-12 (1998).

Ballman's mischaracterizations and errors display an obvious failure to attain the heightened level of intellectual rigor required of testifying experts. *Id.* at 238:16-21, 238:22 to 239:5. Her analysis contains numerous substantial errors and unsupported contentions that merit exclusion. *See Moore v. Int'l Paint, LLC*, 547 Fed. Appx. 513, 516 (5th Cir. 2013) (expert analysis with numerous aspects having no support in the record or contradicted by evidence properly excluded).

Finally, Dr. Ballman has an incorrect, unsupported conception of point estimates. Throughout her report, Dr. Ballman referenced point estimates to explain her findings on association. Remarkably, Dr. Ballman rejected the consistent associations found in the observational studies and meta-analyses as "weak or non-existent." JX 41, Ballman Rpt. at 38. Yet generally, a relative risk greater than 1.0 is probative of general causation, meaning a drug has the capacity to cause the disease:

> [A] point estimate serves as a way to calculate a single value for a sample of data and is the researchers' 'best guess' as to the level of risk of a specific health effect from the substance being studied. A point estimate of 1.0 is indicative of no effect; a point estimate above 1.0 is indicative of increased risk; and a point estimate below 1.0 is indicative of decreased risk."

*Accutane*, 191 A.3d at 570 n.17 (citing PX 37, *RMSE* at 292); *see also Bextra & Celebrex*, 524 F. Supp. 2d at 1172-73. But according to Dr. Ballman, "[w]hen assessing the strength of the association, general principles of epidemiology hold that point estimates of less than 1.20 are generally considered to show no association between the drug and the outcome." JX 41, Ballman Rpt. at 38. Her adherence to this principle is incorrect and, as shown below, both arbitrary and contradictory.

According to Dr. Ballman's flawed reasoning, the point estimates observed in Matthews 2016 (OR 1.14) or Lian 2016 (OR 1.18), for example, would equate to a non-existent association between PDE5 inhibitor use and melanoma, since the point estimates are below 1.2. *Id.* at 43 ("Point estimates of 1.0 to 1.2 may be considered 'no association,' with point estimates of 1.2 to 1.5 showing weak association. None of the published studies observed a risk of 2 or greater."). But elsewhere her report cited a publication by the International Agency for Research on Cancer (IARC) concerning the use of UV-emitting tanning devices, such as indoor tanning beds, and the development of melanoma. *Id.* at 14. That study reported an ever-use point estimate of 1.16 (with ten or more uses reporting a point estimate of 1.21). *See id.* Unlike

that of PDE5 inhibitor use and melanoma studies, however, Dr. Ballman deemed this odds ratio is sufficiently strong enough to confirm an association between indoor tanning and melanoma. *Id.*; JX 81, Ballman Dep. at 153:16-17 ("I believe that there is an association with melanoma.").

Dr. Ballman frequently—and improperly—rounded point estimates in an inconsistent and random manner. *Id.* at 141:18 to 143:1. For example, she contended that a 1.47 odds ratio equates to a two-fold increase in melanoma risk to support her claim that skin pigmentation is a risk factor for developing melanoma. JX 41, Ballman Rpt. at 14; JX 81, Ballman Dep. at 139:18 to 143:1. Strikingly, not once in her report does she refer to comparable point estimates reported in the observational studies linking PDE5 inhibitors to melanoma as "two-fold."[46] The practice of rounding point estimates up or down is improper, imprecise and is not a supported methodology.

As shown above, Dr. Ballman is unqualified and offered unreliable opinions. Her testimony should be excluded under *Daubert*.

## VII. DR. BORIS BASTIAN (EXPERT FOR DEFENDANT ELI LILLY).

### A. Dr. Bastian Is Not Qualified by Knowledge, Skill, Experience, Training, or Education to Testify on General Causation.

Dr. Bastian, a dermatologist, pathologist, and melanoma specialist, lacks the qualifications necessary to opine on causality.[47] By his own admission, he is not an epidemiologist, toxicologist or pharmacologist. JX 77, Bastian Dep. at 37. Dr. Bastian did not conduct a Bradford-Hill causality assessment. *Id.* at 40:2-5, 128:7-23. His report failed to even mention Bradford-Hill. *See generally* JX 44, Bastian Rpt. This is not surprising as such an assessment is typically performed by individuals trained and experienced in epidemiology. Dr. Bastian, of course, does not have sufficient experience or education evaluating Bradford-Hill criteria, let alone the qualifications necessary to opine on causality. *Accord Mullins*, 178 F. Supp. 3d at 900 ("Even the most qualified expert may not offer any opinion on any

[46] For example, Loeb 2015 generated an odds ratio of 1.49 for PDE5 inhibitor use with stage 0 melanoma. In addition, Pottegård 2016 reported a 1.47 odds ratio in two high-use analyses. These results were never described by Dr. Ballman as "two-fold" increases.

[47] *See Boris C. Bastian, MD, PhD*, U. CAL. S.F., http://cancer.ucsf.edu/people/profiles/bastian_boris.3307 (last visited Jan. 10, 2019).

subject"; excluding expert opinions beyond expert's area of expertise). Thus, the Court should exclude Dr. Bastian's testimony on causality.

Nevertheless, Dr. Bastian's report and deposition testimony included numerous statements either implying or directly asserting that there is no "causation" or "causal relationship" between PDE5 inhibitor use and melanoma progression. Even if he had the requisite qualifications to assess causality—which he does not—his "causation" opinions are not admissible because he "has not identified any reliable method that he used to form these opinions." *Mullins*, 178 F. Supp. 3d at 901 (*citing Domingo*, 289 F.3d at 607 ("The reasoning between steps in a theory must be based on objective, verifiable evidence and scientific methodology of the kind traditionally used by experts in the field.")). Dr. Bastian conceded that he provided no assessment or methodology in his report:

> Q. [Y]ou didn't do a causal assessment in this report, we know that, correct?
>
> A. What do you mean by "a causal assessment"?
>
> Q. Do you know what a causal assessment is of the science?
>
> A. Well, can you explain it to me?
>
> Q. I just asked you, do you know what one is?
>
> A. Well, I assume it means assessing the cause and effect relationship.
>
> Q. Okay. And you didn't do that in this report, though; isn't that fair?
>
> A. Well, that report, it doesn't allow—oh, you mean my report? Oh, okay. Well, I guess I looked for biologically plausible connection between pharmacologically inhibiting PDE5 and any aspects of melanoma progression.

JX 77, Bastian Dep. at 128:7-23. Because Dr. Bastian failed to elucidate a proper causation methodology, let alone conduct an assessment, this Court should exclude testimony from Dr. Bastian either concluding or suggesting no "causation" exists between PDE5 inhibitor use and melanoma progression.

### B. Dr. Bastian's Opinions on Biological Plausibility Are Based on Unreliable Methodology and Litigation-Driven.

Dr. Bastian's report presumptively opined on the biological plausibility of PDE5 inhibitor use and melanoma progression. Not only did Dr. Bastian clearly misconstrue the concept of biological plausibility, he evaluated scientific studies by a different standard based upon whether the evidence supported Eli Lilly's position—a methodology which is clearly not based on reliable scientific principles, is litigation-driven, and ultimately unreliable. Further, Dr. Bastian employed a far higher standard of "plausibility" than is required. Thus, his opinions on biologic plausibility should be excluded.

#### 1. Dr. Bastian Employed an Improperly Stringent Standard for Biological Plausibility and Ultimately Admitted PDE5 Inhibition Could Bring About Melanoma Progression.

Dr. Bastian made the overreaching claim that there is no evidence to support even the mere possibility that PDE5 inhibition brings about melanoma progression. Dr. Bastian opined that it is not even *possible* that PDE5 inhibition might bring about melanoma invasion or motility—something no reasonable researcher would be able to conclude, especially given the scientific evidence showing potential mechanisms of action, the documented invasion experiments, and the demonstrated associations between melanoma incidence and PDE5 inhibitor use. *See, e.g.*, JX 77, Bastian Dep. at 69:15-22 ("Q: So it's not possible . . . [t]hat a PDE5 inhibitor when used in a person could bring about motility of melanoma cells or invasion of melanoma cells. A: I see **no evidence** that –that supports this.") (emphasis added).

Dr. Bastian, however, contradicted his litigation-driven conclusion that there is "no evidence." First, he acknowledged that experiments conducted in Arozarena actually show increased motility of melanoma cells when PDE5 is inhibited.[48] *Id.* at 73:2-19, 21-25. Second, despite his attempts to downplay significant evidence supporting melanoma effects from PDE5 inhibition, Dr. Bastian admitted that it is possible that PDE5 inhibitors could bring about melanoma progression:

[48] According to Bastian, cell "motility" is a feature of invasion. JX 77, Bastian Dep. at 42:13-17 ("I would say cell motility is a—is a—a feature that is required—one of several features that is required for—for cell invasion.").

> Q: So, Doctor, is it possible that PDE5 inhibition or depletion could bring about increased invasion or accelerated invasion for certain melanoma cells but not others?
>
> A: Well, that's what the data shows.

*Id.* at 11:12-15, 18-19; *see also id.* at 105:4 to 107:4, 8-13.

Dr. Bastian further demonstrated his one-sided, improperly stringent standard when he audaciously testified that the Dhayade 2016 study (a peer-reviewed study, from a world-renowned cGMP laboratory published in a prominent journal, which demonstrates the role PDE5 inhibitors in melanoma progression and the signaling pathway by which this occurs) has no strengths at all:

> Q. So you haven't analyzed whether the Dhayade study has ***any*** strengths before you've sat here today?
>
> A. I have—I haven't—I'm—looked at this way: I've looked at every piece of every experiment that they did and found flaws with many of them. I pointed some out. There are a lot more. And so I—I would—I would—if you forced me to say one way or the other, I—**I would say it doesn't have any strength**.

JX 77, Bastian Dep. at 190:2-11 (emphasis added).

Dr. Bastian admitted his report included unfounded accusations of bias and improper methodology of studies showing a cancer effect from PDE5 inhibition. He did not make the same unfounded accusations of studies which he believes support his notion that PDE5 inhibitors have an anti-cancer effect. Particularly as to Dhayade 2016, Bastian made unfounded claims of lack of confirmation of cell lines, observer bias, and blinding. JX 44, Bastian Rpt. at 30 (lack of confirmation of cell lines and blinding), *id.* at 31 (lack of blinding and observer bias), *id.* at 81 (lack of blinding). Yet, Dr. Bastian admitted he does not know whether Dhayade 2016 used blinding. JX 77, Bastian Dep. at 94:7-11. Dr. Bastian further agreed that confirmation of proper methodology such as blinding and contamination is typically part of a peer review process prior to publication. *Id.* at 94:17-18, 95:7-10 ("scientific rigor…has increased significantly over the last few years [. . . and] editorial review from the journals has definitely increased in stringency significantly, especially since Arozarena [2011] has been published.").

The manner in which Bastian selectively rejected scientific findings showing a link between PDE5 inhibition and melanoma progression while highlighting specious results further demonstrates the litigation-driven nature of his conclusions. He routinely praised experiment results supporting his conclusions which lacked statistical significance while entirely ignoring statistically significant results linking PDE5 inhibition to melanoma progression. *See, e.g.*, JX 77, Bastian Dep. at 112:22 to 113:2 (cherry-picking results in Arozarena he believed support his opinion that PDE5 inhibitors have anti-cancer effects; rejecting statistically significant findings demonstrating otherwise).

**2. Dr. Bastian Employed a Lax Standard for His Evaluation of Studies He Believes Support His Hypothesis that PDE5 Inhibitors Have Anti-Cancer Effects.**

Dr. Bastian did not employ such stringent standards to the literature he believes demonstrates anti-cancer effects of PDE5 inhibitors. Dr. Bastian was critical of Arozarena showing that PDE5 inhibition leads to a statistically significant increase in invasion of melanoma when PDE5 is decreased by both pharmacological inhibition and genetic knockdown. He condemned the results as contradictory and claimed only *four* of *ten* cell lines show a pro-invasive effect from PDE5 inhibitors. JX 77, Bastian Dep. at 112:22 to 113:2. But when he evaluated studies he claimed support an anti-cancer effect of PDE5 inhibitors, his formerly rigorous analysis became very thin.

For example, Dr. Bastian claimed the Hassel 2017 study shows "some signal" that PDE5 inhibitors are an effective anti-cancer drug when only *three* of *twelve* patients achieved stable disease in a hypothesis generating trial with no control. Dr. Bastian further downplayed the lack of statistical significance in Hassel 2018 and attempted to explain away the statistically significant melanoma effects demonstrated in Arozarena and Dhayade. *See id.* at 219:3, 220:8-22.

Dr. Bastian relied on studies that do not relate to melanoma to support his anti-cancer opinion for PDE5 inhibitors. Yet, he refused to acknowledge evidence of cancer effects of PDE5 inhibitors in *melanoma* cell lines. This is an improper and litigation-driven methodology. Dr. Bastian himself admitted that cancers are different. *Id.* at 193:20-22. He further conceded that cancers behave differently and even react differently to compounds and drugs and even acknowledged the principle that one cannot extrapolate

the results of studies in other cancers to melanoma. *Id.* at 194:12 to 197:24, 200:23 to 201:1. Yet, despite these concessions, he married himself to his improper, conclusion-driven methodology: ". . . So I don't agree with the generalization, but more specifically, I say the results in the literature don't lead me to conclude there's anything different in melanoma than the other cancers." *Id*. at 201:10-14.

In addition to improperly relying on studies that do not address melanoma, Dr. Bastian also relied on studies of less specific, less selective, PDE inhibitors to support his anti-cancer theories. Sildenafil and tadalafil are highly specific and highly selective inhibitors of PDE5. Zaprinast and Dipyridamole are not. Dr. Bastian conceded that the specificity and selectivity of the PDE5 inhibitor tested in a particular study is an important consideration:

> Q: [W]hy is that important?
>
> A: Because if you want to study PDE5 you want to hit PDE5 for the reasons—in your—in your prior question, you asked me why that is important to consider. Yes, if you want to study PDE5 you want to inhibit only PDE5. You don't want to use a drug at a concentration, even a specific PDE5 inhibitor, where you exceed that concentration at the IC50 and risk hitting other PDEs, at least when you can no longer conclude that your—any observed effect is due to the inhibition of PDE5.

*Id.* at 204:16 to 205:2; *see also id.* at 203:17-21.

When explaining why he relied on the Murata study dealing with less selective, less specific PDE inhibitors Dipyridamole and Zaprinast, Dr. Bastian acknowledged the results of such studies could be due to effects off-target from PDE5:

> A: [T]hey may—may have broader effects, but the result in melanoma cells is similar as those with narrower effect. So I have no reason to conclude that I can explain these results or these results could be due to—to off-target effects. They could be, but they are concordant with the results with the more specific inhibitors.

Bastian Dep. at 206:6-13. Dr. Bastian finally conceded that he could not say whether the results would have been the same had sildenafil or tadalafil been tested. JX 77, Bastian Dep. at 210:7-10.

Dr. Bastian evaluated results demonstrating melanoma effects from PDE5 inhibition with such a rigorous analysis that no experiment could pass muster. In stark contrast, Dr. Bastian applied an entirely different, and extremely lax, analysis as to studies he claims support his anti-cancer theories. Such an evaluation of the evidence is clearly litigation-driven, is not proper methodology, and is entirely unreliable.

### 3. Dr. Bastian Provided Litigation-Driven Opinions Demonstrated by his Change in Position in this Case.

Prior to submitting a report in this case for Eli Lilly, Dr. Bastian held much different opinions. In September 2016, Plaintiffs' counsel was in the process of meeting with potential experts and had multiple conversations with Dr. Bastian. Plaintiffs' counsel formed a confidential relationship with him, providing him with Plaintiffs' confidential theories and understandings of the scientific evidence relating to general causation. As part of this confidential relationship, Plaintiffs' learned that Dr. Bastian agreed with Plaintiffs' views of the science linking PDE5 inhibitor use to melanoma development. *See* Plaintiff Executive Committee's Motion to Disqualify Proposed Expert Dr. Boris C. Bastian (Doc. 783). Further, Dr. Bastian agreed to serve as an expert on behalf of *Plaintiffs* in this case at a rate of $800 per hour. *Id*. Just prior to a scheduled in-person meeting between Plaintiffs and Dr. Bastian, Dr. Bastian notified Plaintiffs' counsel that he would no longer consult with Plaintiffs in this litigation yet provided no explanation. *Id*. Two years later, on October 3, 2018, Dr. Bastian was deposed as an expert and offered opinions on general causation in this case. His opinions, however, had changed. His hourly rate up to $1,200, Dr. Bastian now supported Eli Lilly's interpretations of the scientific evidence. *See generally* JX 44, Bastian Rpt.

Clearly, Dr. Bastian had agreed both to work with Plaintiffs and with Plaintiffs' views of the scientific evidence. Coupled with his suspect methodology, Dr. Bastian's sudden about face upon his $400 hourly pay increase is demonstrative of litigation-driven conclusions that are rightly excluded.

## VIII. DR. MARCUS BOSENBERG (EXPERT FOR DEFENDANT ELI LILLY).

### A. Dr. Bosenberg Is Not Qualified by Knowledge, Skill, Experience, Training, or Education to Testify on General Causation.

Dr. Bosenberg is not an epidemiologist qualified to testify on general causation. He is dermatologist, pathologist, immunology professor, and practicing dermatopathologist, with degrees in chemistry and physics. JX 47, Bosenberg Rpt. at 1-2. He is not an epidemiologist, toxicologist or pharmacologist. *Id.* In offering his opinions in this case, he was simply asked to "evaluate the biological plausibility that PDE5 inhibitors might increase melanoma formation or progression." JX 79, Bosenberg

Dep. at 20:5-9. He was not asked to—nor did he—perform any sort of causality assessment. He did not do a Bradford-Hill causality assessment, nor did he even understand what such an assessment is. None of Dr. Bosenberg's qualifications demonstrate he has sufficient experience or education with Bradford Hill. *Accord Mullins*, 178 F. Supp. 3d at 900 ("Even the most qualified expert may not offer any opinion on any subject"; excluding expert opinions beyond expert's area of expertise).

Despite this, Dr. Bosenberg made statements either implying or directly asserting that there is no "causation" between PDE5 inhibitor use and melanoma progression. Such statements should be excluded. As described above, Dr. Bosenberg did not perform a causal assessment and provided no methodology. Dr. Bosenberg further confirmed at his deposition that he provided no assessment or methodology in his report:

> Q. Where in your report does it discuss your methodology for coming to your causation conclusion?
>
> A. Let me go back to the very end in terms of a statement related to that. So my statement related to causation, I believe, is in the third-to-last paragraph above my signature and it refers to plaintiffs' expert causation opinions, and I'm stating that I do not agree with those causation conclusions.

JX 79, Bosenberg Dep. at 250:10-19. The third-to-last paragraph of Dr. Bosenberg's report is far from a proper causal assessment and includes no mention—let alone application—of a methodology. The paragraph is only three sentences long. It does not mention Bradford-Hill or any other causal criteria. It simply notes disagreement with Plaintiffs' causation opinions declaring there is no biological plausibility by criticizing reliance on B16 melanoma cell lines and dose levels used in underlying mechanistic studies. JX 47, Bosenberg Rpt. at 74.[49] As such, any opinions from Dr. Bosenberg on causation are not the product of reliable principles and methods and should be excluded under *Daubert*.

**B. Dr. Bosenberg Employed an Incorrect Standard for Biological Plausibility.**

Dr. Bosenberg's report purports to provide an opinion on the biological plausibility of PDE5 inhibitor use and melanoma progression. Dr. Bosenberg, however, did not appear to grasp concept of

[49] Dr. Bosenberg provides no causal assessment elsewhere in his report. Nor does he outline any methodology for coming to a conclusion on causality. A word search of his report reveals no instances of the words "Bradford" or "Hill." *See generally* JX 47, Bosenberg Rpt.

biologic plausibility. In particular, Bosenberg did not understand that biological plausibility and general causation are two separate considerations requiring two separate analyses. He erroneously conflated the biological plausibility factor with the causation assessment, repeatedly asserting there is no "biologically plausible causal relationship" or "biologically plausible causal mechanism." JX 47, Bosenberg Rpt. at 34, 35, 44, 61. This ignores, however, that biologic plausibility is just one of the many considerations in whether the observed association could be scientifically plausible. *See* PX 37, *RMSE* at 604-05.

> Biologic plausibility is just one factor in causation analysis. To say that a cause and effect relationship is plausible is not to offer an opinion about the likelihood that such a relationship actually exists. Biologic plausibility opinions reflect only the expert's belief that a theory is coherent with existing knowledge, not that the theory is correct. *See Reference Manual on Scientific Evidence* 378 (the salience of biologic plausibility in evaluating causation depends "on the extent of scientific knowledge about the cellular and subcellular mechanisms through which the disease process works.").

*In re Zicam Prods. Liab. Litig.*, 2011 WL 798898, at *112 (D. Ariz. Feb. 24, 2011).

Dr. Bosenberg further exposed his lack of knowledge of the concept of biologic plausibility by demanding a far higher standard than what is required in order to find the existence of this factor. For example, Bosenberg declared (incorrectly) that *in vitro* studies "do not establish in themselves actual effect, *or a biologically plausible potential effect*, in humans. JX 47, Bosenberg Rpt. at 7 (emphasis added) (providing no citation for such a proposition); *see also id.* at Section III.A.3. (entitled "Pre-clinical testing does not accurately predict effects in human patients"). Dr. Bosenberg is incorrect in concluding that a *known* human mechanism must be established before biological plausibility is established. Such proposition is contrary to accepted scientific principles, contradicts the legal and scientific authorities cited herein (which do not require certainty), and should be excluded. *Accord* PX 43, Weed & Hursting (1998) (distinguishing between a *plausible* mechanism (proper standard) and a *known* mechanism (too strict of a standard)). Because Dr. Bosenberg clearly applied the wrong standard in his evaluation of biological plausibility, his resulting conclusions are unreliable and merit exclusion.

**C. Dr. Bosenberg Engaged in Improper Cherry-Picking.**

Dr. Bosenberg demanded confirmation of physiologic relevance for study results that contradicted his views of the effects of PDE5 inhibitors while he conveniently (for him) ignored the lack of any such confirmation for results that fit his views. For example, he rejected PDE5 signaling study results, Figures 7A-7J in Arozarena 2011, because they never demonstrated "that the level of forced PDE5 re-expression has any physiologic relevance." *See* JX 47, Bosenberg Rpt. at 42-44. Yet, when Arozarena 2011 tested PDE5 inhibitor use in mice and measured no resulting growth, Dr. Bosenberg accepted such results as conclusive proof of anti-tumor properties of PDE5 inhibitors even though Arozarena 2011 never even tested whether the dose of sildenafil provided to the mice was even high enough to bring about the expected physiologic response (increased cGMP). *See id*. at 42-44 (referencing Arozarena 2011, Figure 7K).

This flaw further demonstrates that Bosenberg did not operate under a basic scientific concept: that the absence of evidence is not evidence of absence. In order to demonstrate that the results from Arozarena 2011's Figure 7K are actually evidence of an absence of effect (i.e., evidence that sildenafil does not increase melanoma tumor lung weight), Arozarena 2011 would have had to confirm that the amount of sildenafil provided to the mice actually had the expected physiologic response—that is, that the dose was high enough to increase the cGMP levels in the mice. Arozarena 2011 never performed such a test. As such, there is no data to support the claim that Arozarena provided an appropriate dose, and Figure 7K is (at best) simply "absence of evidence."

In Dhayade 2016, however, the researchers actually measured whether the dose of sildenafil provided to the mice brought about the expected physiologic response of increasing cGMP levels—which it did—by measuring a sampling of cardiac tissue from the mice. *See* JX 87 at Figure 6E (confirming increased cGMP levels in the mice given sildenafil compared to control mice not given sildenafil), Figure 6F (showing statistically significant increased melanoma tumor volume in the mice given sildenafil compared to control mice not given sildenafil). Such unexplained contrasts in Dr. Bosenberg's views on dose in these two *in vivo* studies are clear evidence that he selectively cherry-picked the results that he felt supported his view on the *in vivo* studies, regardless of what the evidence actually showed. Dr.

Bosenberg's opinions on the *in vivo* dosing of these two studies thus fall short of this Circuit's standard on reliability and should be excluded.

## IX. DR. SAMUEL COHEN (EXPERT FOR DEFENDANT ELI LILLY).

### A. Dr. Cohen's General Causation Opinions are Unreliable.

Dr. Cohen's general causation analysis is deficient and does not support his opinion that PDE5 inhibitors do not and cannot cause an increase in melanoma growth and invasion. First, Dr. Cohen was unable to articulate the methodology he utilized in formulating his opinions and he never once described the methodology in his report. Second, he performed an incomplete analysis and failed to consider the totality of scientific evidence. Dr. Cohen conducted, at best, a very thin Bradford-Hill analysis. Third, Dr. Cohen gave inconsistent opinions concerning the appropriateness of animal dosing, which renders his opinions confusing, unreliable and inadmissible. As opposed to formulating his own independent opinions concerning biological plausibility or a causal relationship between PDE5 inhibitor use and melanoma, Dr. Cohen's report and testimony is focused almost entirely on refuting Dr. Piazza's opinions. Therefore, Dr. Cohen's opinions are unreliable, do not assist the trier of fact and should be excluded in their entirety.

### B. Dr. Cohen Did Not Employ a Proper Methodology.

Dr. Cohen admitted that whenever he publishes literature, there is always be a section that describes the methodology that he employed. JX 83, Cohen Dep. at 145:17-21; 146:18-22. However, here, a methodology section is glaringly absent from Dr. Cohen's report. *See generally* JX 50, Cohen Rpt. Equally problematic, Dr. Cohen was unable to provide any substantive testimony concerning the methodology that he utilized in his report; only providing a generic explanation:

> A: [T]he way I did the report was—**is really not explicitly described**, but stated here is that I performed the same kind of evaluation I would for any scientific evaluation, first going through the literature, then you evaluate the literature and the quality of the studies, and if the quality justifies a further analysis, you do a further analysis, which involves an implementation of the mode of action framework that I've been involved with for over 20 years.

JX 83, Cohen Dep. at 121:13-25 (emphasis added).

When asked further questions about his analytical process, Dr. Cohen referred to his report in which he stated he "employed the same methodological approach and degree of rigor in my work in this

matter as I do in all of my medical and scientific work." JX 50, Cohen Rpt. at 1. Dr. Cohen did not offer any additional insight into his undocumented methodology during his deposition.

Ultimately, Dr. Cohen's "assessment" of causality is lacking. He failed to complete a Bradford-Hill analysis. In fact, his report does not mention Bradford Hill once, nor does he explicitly discuss or analyze any of the factors in his report. *See generally id*.; *see also* JX 83, Cohen Dep. at 52:4 to 53:1. Perhaps recognizing the deficiencies in his report, at his deposition, Dr. Cohen claimed to have considered (1) strength of evidence, (2) consistency, (3) coherence, (4) dose response, (5) biological plausibility and "to some extent analogy and experimentation." JX 83, Cohen Dep at 53:2-10. But even assuming *arguendo* his claims are true, at best, he only considered five of the nine Bradford-Hill factors and making his analysis incomplete.

### C. Dr. Cohen Failed to Analyze and Consider the Totality of Relevant Scientific and Medical Evidence.

Dr. Cohen's review and consideration of the materials provided to him was deficient. In response to questions about the materials he considered in formulating his opinions, Dr. Cohen testified that he received much of the material before writing his report and stated that he would "look at the front page of the documents and decide whether it was something whether he had to review or not." JX 83, Cohen Dep. at 100:12-22. Dr. Cohen admitted that if a particular paper does not pass the "sniff test," he did not need to read it thoroughly. *Id.* at 133:14-23. Dr. Cohen further conceded that he did not perform as extensive of an analysis as he would have normally done, blaming his failure to do so on the "quality of the papers." *Id*. at 124:14-20. Indeed, he readily dismissed the Arozarena 2011 and Dhayade 2016 studies without any substantive explanation and admits that he did not conduct an extensive analysis:

> A: The Dhayade study is—should be dismissed completely. It's not a good study. There's nothing about it that's methodologically proper. Arozarena has some interesting findings but has not been able to be reproduced by a number of things…it is internally not consistent in the findings. So based on that **I didn't go through an extensive analysis and mode of action human relevance, because the findings in those papers didn't warrant an evaluation to that extent.**"

*Id*. at 123:6-18 (emphasis added).

Dr. Cohen could not identify many of the materials he considered in formulating the opinions expressed in his report. He admitted that he relied on information not identified in the report but could not recall the names of journal articles and other materials cited. *Id*. at 81:14-25, 82:1-8, 83:24-25, 84:1-2. Dr. Cohen also acknowledged that he improperly neglected to cite to everything that he reviewed or looked up to support his opinions. *Id*. at 84:1-25; 85:1-25; 86:1-9.

Dr. Cohen failed to perform a comprehensive literature search and analysis. Indeed, Dr. Cohen conceded that he did not read the materials thoroughly when he described his review process:

> A: I might also read that this is a—like in some of the reports I think there was some clinical investigations that—**some of them I would only read like the summary**, which would give me enough information to say that is not going to influence what I am going to write because it's not a topic. So fairly—you can **fairly quickly scan** through a large number of documents to decide whether it is going to be important or not. Same way you do a literature search. You know, a literature search on a topic can come up with hundreds to thousands of publications, and **you just have to go through and screen them primarily by title, but sometimes you have to read the abstract as well**.

JX 83, Cohen Dep. at 101:20 to 102:15 (emphasis added). In addition, Dr. Cohen admitted he did not read Eli Lilly's documents in their entirety yet claimed to rely on them in formulating his opinions. *Id*. at 104:17-20.

Critically fatal to his opinions, Dr. Cohen failed to consider and analyze the totality of scientific evidence, particularly the human studies/epidemiology related to PDE5 inhibitors and melanoma. Dr. Cohen admitted that the better epidemiology studies are prospective cohort studies, yet he did not discuss the Li 2014 study or perform an analysis of it in his expert report. *Id*. at 180:17-25, 181:1-3. Dr. Cohen further admitted that the Li 2014 study secondary analyses showed more than a doubling of the risk of melanoma. *Id*. at 188:20-25. Despite these concessions, Dr. Cohen nonsensically excluded the Li 2014 study from his own analysis, which casts serious doubt on his methodology. Moreover, even though statistically significant results were found in many other studies, and notwithstanding the fact that authors of observational studies found the association between PDE5 inhibitor use and melanoma to be biologically plausible, Dr. Cohen failed to appropriately consider, analyze, discuss, or even refute any of

the relevant epidemiological literature, which consistently shows an association between PDE5 inhibitor use and melanoma.

Given Dr. Cohen's inability to explain his own methodology, his thin (at best) causation "assessment," and his admittedly deficient analysis of materials, his opinions concerning biological plausibility and causation are unreliable. Accordingly, these opinions do not assist the trier of fact and should be excluded.

**D. Dr. Cohen Renders Inconsistent and Contradictory Opinions on Animal Dosing.**

Finally, Dr. Cohen improperly criticized the credibility of Dhayade 2016 study, specifically claiming that the dosing was excessive. However, he testified that the threshold or floor for animal dosing is at least 25 times higher than human exposure. He further admitted that higher dosing in animals is industry standard and generally accepted:

> A: This is the FDA and ICH requirement, actually, that—they prefer that they be at least 25 times the human exposure, but in some circumstances the realization is that cannot be attained….but that's the goal."

JX 83, Cohen Dep. at 75:1-25; *see also* JX 50, Cohen Rpt. at 10.

Dr. Cohen also cited to the Brambilla study in support of the opinions in his report, which he admitted was a reliable publication. JX 83, Cohen Dep. at 72:15-23. However, the Brambilla paper studied tadalafil in a carcinogenesis assay at a 400mg a day dosage in animals, which is 20 times higher than the highest recommended dose in humans for treating erectile dysfunction (20mg). *Id*. at 76:7-20. Inconsistent statements such as these raise the significant risk of confusing the jury and substantially weaken Dr. Cohen's opinions concerning the appropriateness of animal dosing in assessing carcinogenesis, making these opinions unreliable and inadmissible.

**E. Dr. Cohen's Industry Bias Undermines the Reliability of His Opinions.**

Dr. Cohen should be disqualified from giving any opinions in this litigation because he has substantial industry bias. He is currently performing research work which is funded by Pfizer. JX 83, Cohen Dep. at 29:9-20. In addition, in 2012, Dr. Cohen was paid by Pfizer to serve as the principal investigator for work related to human vascular tumors, and he also served on Pfizer's advisory board

between 2000-2005. *Id*. at 38:24-25, 39:1-7. He also admitted that publication bias and funding bias can influence the interpretation of results, even though he failed to disclose his conflict of interests or funding bias in his own publications. *Id*. at 67:14-19.

Dr. Cohen has exclusively testified on behalf of industry and has done so several times. He admits to testifying six times at trial and seven times in depositions for defendant drug companies or chemical companies. *Id*. at 7:22-25, 8:1-19. He has never testified for any plaintiff at deposition or trial that any pharmaceutical drugs can cause cancer. *Id*. at 14:3. Dr. Cohen has received considerable remuneration for his testimony on behalf of industry; he admitted to having received over $200,000.00 for his testimony in the Actos mass tort litigation. *Id*. at 44:10-10.

Moreover, Dr. Cohen is and has been a paid consultant for pharmaceutical and chemical companies, including Defendant Pfizer, more than 20 or 25 times. JX 83, Cohen Dep. at 14:4-24; *see also id.* at 19:25, 26:22-25, 27:1-4, 27:10-14 (Dr. Cohen has also been a paid consultant for Schering Plough, Sanofi Aventis and AstraZeneca (advisory board member)). He has received millions of dollars in grants from industry. Dr. Cohen admitted that out of 55 grants, only about 15 are not from chemical or pharmaceutical companies. *Id*. at 114:19-25, 115:1-2.

For each of the foregoing reasons, this Court should preclude Dr. Cohen from offering general causation and biologic plausibility opinions at trial.

## CONCLUSION

Plaintiffs respectfully request the Court grant their Motion to Exclude Certain of Defense Experts' Opinions.

1. **The opinions of Dr. Joseph Califano (expert for Defendant Pfizer) should be excluded**. Dr. Califano is unqualified to offer expert testimony on epidemiological studies. Even if he was qualified—which he is not—Califano did not employ a reliable methodology to support his proffered opinions on general causation. As for his proffered opinions on biologic plausibility, they do not assist the trier of fact. Finally, his opinions should be excluded due to his cursory and selective review of materials.

2. **The opinions of Dr. Richard Marais (expert for Defendant Pfizer) should be excluded**. Dr. Marias proffered opinions on biologic plausibility that are inconsistent with his prior published work,

are litigation-driven, and are unreliable. In addition, these opinions should be excluded because they are based on an incorrect standard of plausibility. As for his proffered opinions on epidemiology and general causation, they should be excluded due to his lack of qualifications—Dr. Marias is not an epidemiologist. Even if he was qualified to offer a causation opinion, he did not apply any methodology, let alone a reliable one, for his proffered general causation opinions.

3. **The opinions of Dr. Lynn Schuchter (expert for Defendant Pfizer) should be excluded**. Dr. Schuchter's proffered opinions are unreliable. She utilized no clear methodology. Further, they should be excluded because she offered no analysis of her own—she merely re-stated the analyses and conclusions of studies without offering a substantive assessment of them.

4. **The opinions of Dr. Maria Wei (expert for Defendant Pfizer) should be excluded**. Dr. Wei is not qualified to opine on causality. She provided little to no analyses, did not conduct a causality assessment, and utilized no methodology to form her opinions on causality.

5. **The opinions of Dr. Karla Ballman (expert for Defendant Eli Lilly) should be excluded**. Dr. Ballman is not qualified to give an epidemiology opinion. She is not an epidemiologist. She lacks the requisite expertise necessary to proffer causation opinions, especially on melanoma—a cancer about which she lacks adequate knowledge. Even if she was qualified—which she is not—she did not employ a reliable methodology to reach her causality conclusions. Further, her opinions on confounding should be excluded because she demonstrated a lack of requisite expertise on the concept of confounding factors. Likewise, her proffered opinions on biologic plausibility should be excluded as unreliable and unsupported. She is not qualified to examine the mechanisms at issue, did not understand the plausibility standard, and did not perform an adequate analysis. Finally, her report made a number of substantial errors rendering her opinions unreliable.

6. **The opinions of Dr. Boris Bastian (expert for Defendant Eli Lilly) should be excluded**. Dr. Bastian is not an epidemiologist and is not qualified to testify on causation. He provided no methodology and he performed no analysis of causality. Also, his proffered opinions on biological plausibility are litigation-driven and based on improper methodology. His standard for plausibility is

incorrect and inconsistent with his standard for the plausibility of possible anti-cancer effects of PDE5 inhibitors.

7. **The opinions of Dr. Marcus Bosenberg (expert for Defendant Pfizer) should be excluded**. Dr. Bosenberg is not an epidemiologist and is not qualified to testify on causation. He provided no methodology and he performed no analysis of causality. As for biological plausibility, he employed an incorrect standard requiring certainty. Further, Dr. Bastian's cherry-picking and incorrect analysis of study results render his opinions unreliable.

8. **The opinions of Dr. Samuel Cohen (expert for Defendant Pfizer) should be excluded**. Dr. Cohen's proffered opinions on causation are unreliable. He could not articulate the methodology he utilized, he performed an incomplete analysis, and he failed to consider the totality of available evidence. His opinions on dosing should also be excluded as they are inconsistent and contradictory. Finally, his extreme bias undermines the reliability of all his conclusions.

Dated: January 11, 2019.

CORY WATSON, P.C

*/s/ Ernest Cory*
Ernest Cory (*Admitted Pro Hac Vice*)
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*/s/ Munir R. Meghjee*
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*On Behalf of Plaintiffs Executive Committee*

*/s/ Jennifer Liakos*
Jennifer Liakos
NAPOLI SHKOLNIK PLLC

*On Behalf of Plaintiffs Steering Committee*

**ATTESTATION PURSUANT TO CIVIL L.R. 5.1(i)(3)**

I, Ernest Cory, hereby attest that concurrence in the filing of this document has been obtained from the other signatories.

Dated: January 11, 2019.

*/s/ Ernest Cory*
Ernest Cory

**CERTIFICATE OF SERVICE**

I, Rachel Abrams, hereby certify that on this 11th day of January 2019, I electronically filed the foregoing with the Court using the CM/ECF system and thereby delivered by electronic means to all registered participants as identified on the Notice of Electronic Filing.

*/s/ Rachel Abrams*
Rachel Abrams